

## EDITORIAL

### Modern Times

are fast. The shortest possible **publication times** are demanded from scientific journals. Whenever there is a choice between speed and quality, speed all too often wins—this is also true in science, even when the research results are not to be patented. Here, however complaining does not help; a journal such as *Angewandte Chemie* must meet the challenge to combine quality and speed. On the one hand, between 1998 and 2001, the *average* publication time for Communications, from submission to electronic and print release—which are only a few days apart for *Angewandte Chemie*—was reduced from around 190 to about 150 days, and we won't stop there! On the other hand, the consistent efficiency of a strong editorial team ensures that particularly important work in competitive areas is published extremely rapidly. Thus, the last issue of 2001 contains two Communications by Patrick Harran et al. on the total synthesis of nominal diazonamides which first arrived in the editorial office on November 15th: The time between submission and electronic publication was 29 days, and between submission and print was 32 days. In this period, both manuscripts were reviewed by three referees, revised by the author, and processed by the editorial office; in addition the author and editors were able to check the galley proofs and the page proofs, so that the quality was not compromised in any way.

### COMMUNICATIONS

Although this **fast track** has in the past been used occasionally, it should, as from the next issue, be a regular feature of *Angewandte Chemie*. Very Important Papers (VIPs) and Hot

Papers, which until now have been presented only with a short text on our homepage ([www.angewandte.com](http://www.angewandte.com)) long before the actual publication, will in future be placed in the first available issue after their acceptance. The publication time will thus more than ever be determined by the refereeing process and the time authors take to revise a manuscript.

**Ephemerality** is the sister of rapidity: Electronic publishing makes it possible to analyze the number of “hits” on a single article and shows that 90% of the hits are within the first three months of publication. However, the number of hits at *Angewandte Chemie* after the first three months, are still far higher than for other journals, and the review articles are accessed most often. The classic **Reviews** in *Angewandte Chemie* are a proven antidote against ephemerality in chemistry. The importance of the Reviews has in no way been diminished by the more recent supplementary shorter forms (**Essay** and **Minireview**). The distinction between the different contributions to *Angewandte Chemie* are outlined

Table 1. Origin of communications from January to November 2001. Manuscripts with authors from several different countries were assigned to the country of the submitting author.

| Country         | Number |
|-----------------|--------|
| USA             | 373    |
| Germany         | 337    |
| Japan           | 272    |
| China           | 210    |
| UK              | 105    |
| France          | 93     |
| South Korea     | 71     |
| India           | 67     |
| Spain           | 67     |
| Italy           | 56     |
| Switzerland     | 52     |
| Canada          | 48     |
| The Netherlands | 30     |
| Israel          | 26     |
| Taiwan          | 25     |
| Australia       | 16     |
| Belgium         | 13     |
| Singapore       | 13     |
| Poland          | 11     |
| Sweden          | 11     |
| Others          | 61     |

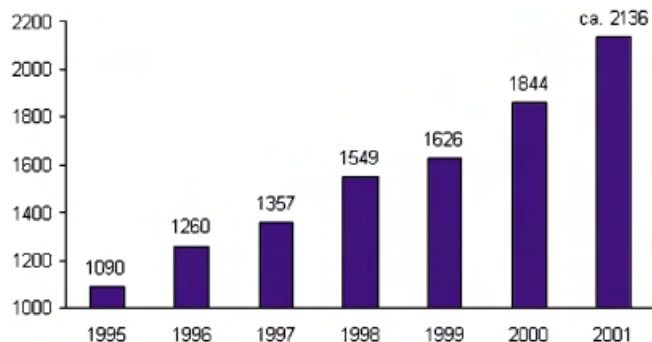


Figure 1. Number of communications submitted to *Angewandte Chemie* from 1995 to 2001.

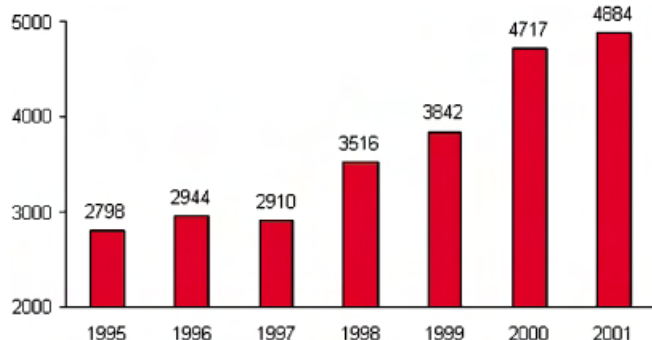


Figure 2. Total number of pages published in *Angewandte Chemie International Edition* from 1995 to 2001.

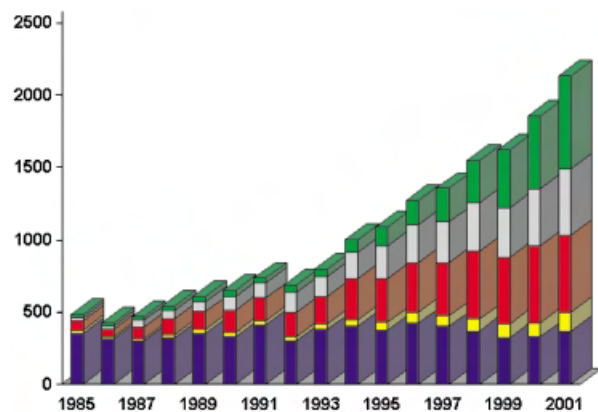


Figure 3. Regional origins of submitted communications between 1985 and 2001 (the figures for this year have been extrapolated on the basis of the numbers for the first eleven months). Color coding: blue: Germany, red: Western Europe, gray: North America, green: East Asia, yellow: other countries.

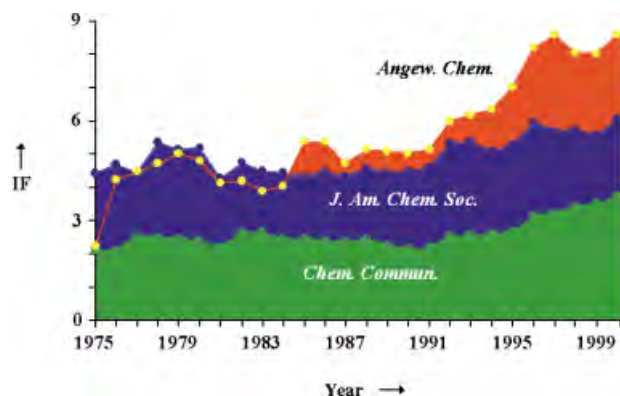


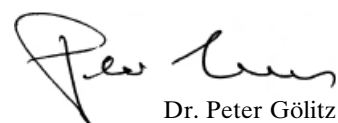
Figure 4. Development of the Impact Factors (IF) of *Chemical Communications*, *Journal of the American Chemical Society*, and *Angewandte Chemie* since 1975.

in the *Concise Notice to Authors* on our homepage and after the Table of Contents in this issue. The *Guidelines for the Preparation of Manuscripts* is now only available on our homepage; these should be consulted while preparing a manuscript, as a correctly formatted submission can be processed more rapidly. We gladly accept manuscripts that are sent by e-mail, although such submissions should ideally consist of a maximum of four files (manuscript with incorporated graphics, graphical material, and supporting information as compressed PDF files, and an accompanying letter).

Not only do authors want fast publication times, readers want rapid uptake of information! Too often, the reader jumps hastily from the title to the introduction and on to the summary, before proceeding straight to the next article. In future, to cater better for the needs of the **speed reader**, the sections at the beginning and at the end of publications will be presented in a more reader-friendly manner (see also the *Concise Notice to Authors*).

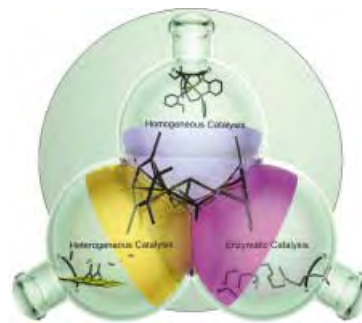
Modern times are also times of deception, and science is no exception. "Minor" deceptions come to the fore: missing and/or misleading literature citations, concealment of own related publications upon submission, double submission of the same work to different journals, and unethical use of information by referees for personal advantage are just a few of the transgressions that the editorial office has to deal with. All these **transgressions** are addressed in the "Ethical Guidelines to the Publication of Chemical Research" by the American Chemical Society; these internationally accepted rules are regarded as binding at *Angewandte Chemie*.

In spite of everything, modern times are also times of openness and **transparency**. To finish, an overview of the last year at *Angewandte Chemie* follows. By the end of November, at the time of writing this editorial, we had already received 100 more Communications than in the whole of the year 2000, that is, manuscript submission has risen by about 15% (Figure 1). The rejection rate increased significantly (from 56% to just over 60%); the total number of pages of the journal has grown by ca. 160 pages (Figure 2). Additionally, more manuscripts are being submitted from all around the world (Figure 3). For example, for the first time more than 400 Communications (extrapolated figure) were received from the USA; most striking is the increase in submissions from the People's Republic of China. Table 1 on the previous page gives an overview of the origin of manuscripts according to country (January to November 2001). The Impact Factor has also developed positively (Figure 4). But the most important is that we could present lots of wonderful chemistry in *Angewandte Chemie* in 2001, and even more should come in 2002.

  
Dr. Peter Göllitz

# COVER PICTURE

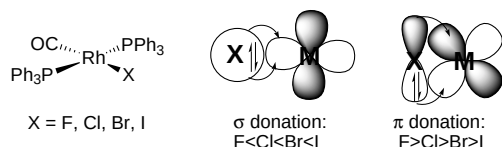
**The cover picture** shows a representation of supramolecular cluster catalysis, which is commonly regarded as a field lying at the interface of homogeneous and heterogeneous catalysis. Homogeneous catalysis is epitomized by Halpern's elucidation of the molecular details of the enantioselective hydrogenation of prochiral alkenes (top flask) catalyzed by a rhodium diphosphane complex. The three-way catalyst is the emblem of heterogeneous catalysis (left flask). The central structure depicts a cluster capable of hydrogenating aromatic substrates under mild biphasic conditions. Most interestingly, the mechanism relies solely on hydrophobic interactions between the catalyst and the substrate. Such weak contacts are reminiscent of enzymatic catalysis as exemplified by triterpene cyclases, which convert squalenes into steroid precursors (right flask). The system described thus lies at the interface of enzymatic, homogeneous, and heterogeneous catalysis. Further details are reported by Süss-Fink et al. on p. 99 ff.



# REVIEWS

Contents

**Tuning catalysts:** varying the halide moiety represents a valuable method of tuning the reactivity and selectivity of halide-containing metal complexes. The differences observed are a product of the steric and electronic properties of the halide ligand which has the ability to donate electron density to the metal center in a predictable manner (see picture). This review discusses the physical properties of various halide–metal complexes and the effect of varying the halide in various transition metal promoted processes. An understanding of the changes that can arise leads to the notion that the metal–halide moiety can be used as a tunable functionality in the design of better transition metal catalyzed reactions.



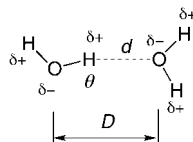
*Angew. Chem.* **2002**, *114*, 26–49

K. Fagnou, M. Lautens\* ..... 26–47

Halide Effects in Transition Metal Catalysis

**Keywords:** asymmetric synthesis • halogens • homogeneous catalysis • ligand effects • transition metals

**A difficult dividing line:** The hydrogen bond is the most important of all the directional intermolecular interactions (see picture). It is understood from modern bonding concepts as a very broad phenomenon with open borders to other interactions, such as covalent bonding, ionic, cation– $\pi$ , and van der Waals interactions. There are dozens of different types of X–H...A hydrogen bonds (A = acceptor) with dissociation energies that span more than two orders of magnitude. This review brings together the research of the last ten years on hydrogen bonds, particularly in the solid state.



T. Steiner\* ..... 48–76

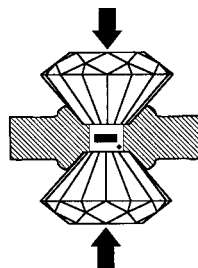
The Hydrogen Bond in the Solid State

**Keywords:** donor–acceptor systems • electrostatic interactions • hydrogen bonds • noncovalent interactions • proton transfer

*Angew. Chem.* **2002**, *114*, 50–80

# MINIREVIEW

**Putting nitrogen under pressure:** The application of high-pressure techniques (for example the depicted diamond anvil cell) allows the synthesis of numerous new materials with useful properties. Recent examples include diazenides, that is, compounds with  $N_2^{2-}$  ions (autoclave techniques),  $\gamma$ - $P_3N_5$ , the first compound with tetragonal  $PN_5$  pyramids (multianvil press), as well as spinel- $Si_3N_4$ , a promising hard ceramic material (shock-wave methods).



E. Kroke\* ..... 77–82

High-Pressure Syntheses of Novel Binary Nitrogen Compounds of Main Group Elements

**Keywords:** high-pressure chemistry • main group elements • nitrides • nitrogen • phase transitions

*Angew. Chem.* **2002**, *114*, 81–86

**Chemistry—recipes for success in the kitchen:** Molecular gastronomy is the part of food science that investigates culinary processes, such as the formation of the two cheese soufflés shown. It is a multidisciplinary approach involving mainly chemistry and physics. Its five main aims are discussed and recent results are given.



*Angew. Chem.* **2002**, *114*, 87–92

H. This\* ..... 83–88

Molecular Gastronomy

**Keywords:** culinary processes • every-day chemistry • food science • molecular gastronomy

## HIGHLIGHT

**Nucleic acids direct chemical reactions.** Recent examples of DNA-templated synthesis suggest that DNA can direct various chemical reactions sequence-specifically and independent of distance in a surprisingly general manner.

*Angew. Chem.* **2002**, *114*, 93–95

D. Summerer, A. Marx\* ..... 89–90

DNA-Templated Synthesis: More Versatile than Expected

**Keywords:** chemical ligation • DNA • oligonucleotides • supramolecular chemistry • template synthesis

## VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.com>

Gold–Xenon Complexes

T. Drews, S. Seidel, K. Seppelt\*

Iron-Catalyzed Polyethylene Chain Growth on Zinc: Linear  $\alpha$ -Olefins with a Poisson Distribution

G. J. P. Britovsek, S. A. Cohen, V. C. Gibson,\* P. J. Maddox, M. van Meurs\*

The Uronium/Guanidinium Peptide Reagents: Finally the True Uronium Salts

L. A. Carpino,\* H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mügge, H. Wenschuh, J. Klose, M. Beyermann, M. Bienert

Expanding Divalent Organolanthanide Chemistry: The First Organothulium(II) Complex and the In Situ Organodysprosium(II) Reduction of Dinitrogen

W. J. Evans,\* N. T. Allen, J. W. Ziller ◆

Nonrelaxable Anisotropic Organization of Organic-Inorganic Hybrid Materials Induced by an Electric Field

G. Cerveau, R. J. P. Corriu,\* E. Framery, S. Ghosh, M. Nobili

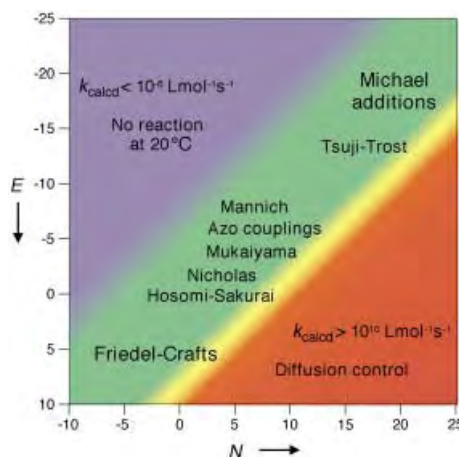
Self-Assembled, Deterministic Carbon Nanotube Wiring Networks

M. R. Diehl, S. N. Yaliraki, R. A. Beckman, M. Barahona, J. R. Heath\* ◆





A **nucleophilicity scale** has been developed that covers 30 orders of magnitude from simple arenes to stabilized carbanions (see picture). Amazingly, the addition of an electrophilicity parameter  $E$  and a nucleophilicity parameter  $N$  is sufficient to predict semiquantitatively the rates of a large variety of organic reactions.



*Angew. Chem.* **2002**, *114*, 97–102

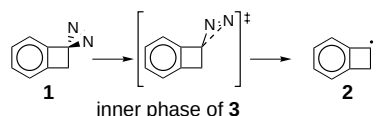
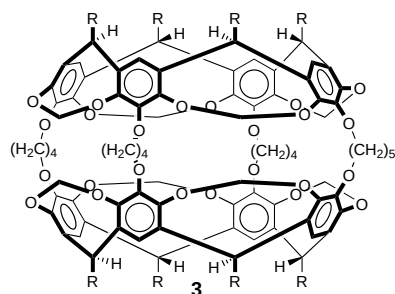
R. Lucius, R. Loos, H. Mayr\* ... 91–95

Kinetic Studies of Carbocation – Carbanion Combinations: Key to a General Concept of Polar Organic Reactivity

**Keywords:** electrophilic addition • linear free-energy relationships • Michael addition • reaction kinetics • substituent effects



**Incarceration strongly increases the rate** of the thermal decomposition of diazirine **1** to yield carbene **2**. The increase of the inner phase rate is rationalized by a stabilization of the transition state through dispersion interactions between the breaking C–N bonds and one of the highly polarizable arene rings of the surrounding host **3**.



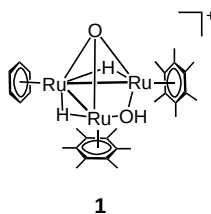
*Angew. Chem.* **2002**, *114*, 102–105

R. Warmuth,\* J.-L. Kerdelhué, S. Sánchez Carrera, K. J. Langenwalter, N. Brown ..... 96–99

Rate Acceleration through Dispersion Interactions: Effect of a Hemiacarcerand on the Transition State of Inner Phase Decompositions of Diazirines

**Keywords:** dispersion interactions • hemiacarcerands • host–guest systems • molecular container • transition states

**At the interface** of homogeneous, heterogeneous, and enzymatic catalysis is the catalytic hydrogenation of benzene to give cyclohexane by the triruthenium cluster **1**. Experimental evidence and molecular modeling studies strongly support a catalytic mechanism in which the aromatic substrate is hydrogenated in the hydrophobic pocket spanned by the three  $\eta^6$ -bound arene ligands without being coordinated to a Ru center.



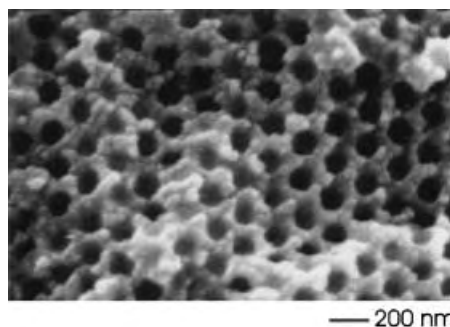
*Angew. Chem.* **2002**, *114*, 105–108

G. Süß-Fink,\* M. Faure, T. R. Ward ..... 99–101

Supramolecular Cluster Catalysis: Benzene Hydrogenation Catalyzed by a Cationic Triruthenium Cluster under Biphasic Conditions

**Keywords:** biphasic catalysis • cluster compounds • host–guest systems • hydrogenation • supramolecular chemistry

**Mesoporous silver with a three-dimensional periodic structure** has been prepared electrochemically (see picture) starting from colloidal crystals immobilized in a hydrogel. In this new process it is possible to tune both the size of the enclosures and the thickness of the walls between the enclosed particles in the mesoscale ordered material.



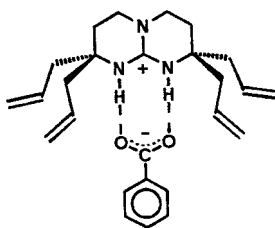
*Angew. Chem.* **2002**, *114*, 108–110

C. Lellig, W. Härtl, J. Wagner, R. Hempelmann\* ..... 102–104

Immobilized Highly Charged Colloidal Crystals: A New Route to Three-Dimensional Mesoscale Structured Materials

**Keywords:** colloids • gels • mesoporous materials • nanostructures • self-assembly

**Lock-and-key binding** is an inadequate description for the molecular-recognition interaction of guanidinium cations and carboxylates in acetonitrile (see picture) as shown by direct calorimetric determinations in a tailored series of host–guest pairs.



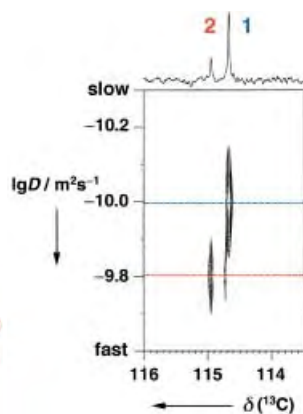
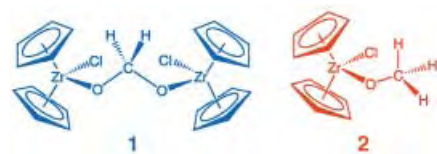
M. Haj-Zaroubi, N. W. Mitzel,  
F. P. Schmidtchen\* ..... 104–107

The Rational Design of Anion Host  
Compounds: An Exercise in Subtle  
Energetics

**Keywords:** bond enthalpy • calorimetry •  
host–guest systems • molecular  
recognition • nitrogen heterocycles

*Angew. Chem.* **2002**, *114*, 111–114

**A new tool** for the investigation of reaction intermediates: By using DOSY NMR spectroscopy, the presence of a binuclear complex **1** as the key intermediate on the way to **2** (see spectrum) was detected for the first time in the title reaction.



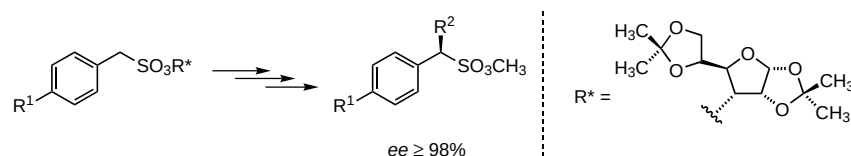
N. E. Schlörer, E. J. Cabrita,  
S. Berger\* ..... 107–109

Characterization of Reactive  
Intermediates by Diffusion-Ordered  
NMR Spectroscopy: A Snapshot of the  
Reaction of  $^{13}\text{CO}_2$  with  $[\text{Cp}_2\text{Zr}(\text{Cl})\text{H}]$

**Keywords:** diffusion • intermediates •  
NMR spectroscopy • organometallic  
compounds

*Angew. Chem.* **2002**, *114*, 114–116

**The right choice of sugar auxiliary led to a breakthrough** in the first asymmetric  $\alpha$ -alkylations of sulfonic acid esters (see scheme). The high asymmetric inductions were reached with 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -D-allofuranose as the auxiliary group, which can be cleaved off again under mild conditions. Enantiopure  $\alpha$ -substituted methyl sulfonates are important building blocks and precursors of bioactive compounds.



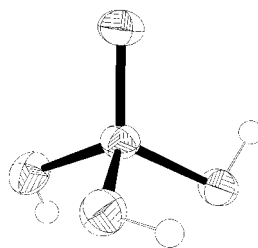
D. Enders,\* N. Vignola, O. M. Berner,  
J. W. Bats ..... 109–111

The First Highly Efficient Asymmetric  
Synthesis of  $\alpha$ -Substituted Methyl  
Sulfonates

**Keywords:** alkylation • asymmetric  
synthesis • carbohydrates • chiral  
auxiliaries • metalation • sulfonates

*Angew. Chem.* **2002**, *114*, 116–119

**The complete protonation** of sulfuric acid, one of the strongest acids, can be achieved with the superacid  $\text{HF}/\text{SbF}_5$ . The salt  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  is isolated at  $-78^\circ\text{C}$  from the reaction of the superacid with bis(trimethylsilyl) sulfate (the structure of the  $\text{D}_3\text{SO}_4^+$  ion in the crystal of the analogous deuterium compound is depicted).



R. Minkwitz,\* R. Seelbinder,  
R. Schöbel ..... 111–114

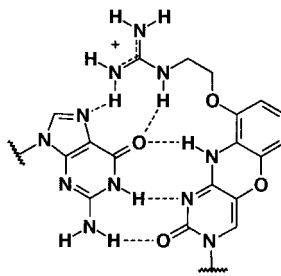
Protonated Sulfuric Acid: Preparation of  
Trihydroxyoxosulfonium  
Hexafluoroantimonate  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$

**Keywords:** IR spectroscopy •  
protonation • sulfuric acid • superacids

*Angew. Chem.* **2002**, *114*, 119–121



**Bound and clamped:** A novel heterocyclic base modification, the guanidino G-clamp, is designed to allow two Hoogsteen-type hydrogen bonds to form between the amino and imino nitrogen atoms of a tethered guanidinium group to O6 and N7 of guanosine, which results in a total of five hydrogen bonds (broken lines, see picture). Details of a crystal structure at 1.0-Å resolution of a modified DNA decamer containing this guanidino G-clamp analogue demonstrate its mechanism of binding.



C. J. Wilds, M. A. Maier, V. Tereshko, M. Manoharan,\* M. Egli\* .... 115–117

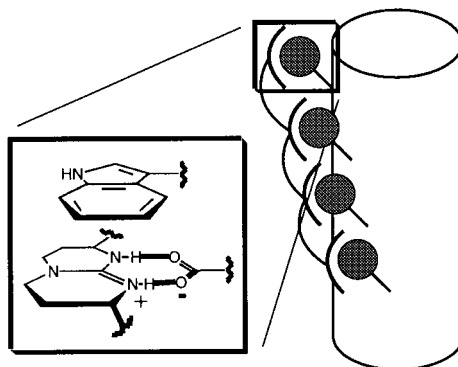
Direct Observation of a Cytosine Analogue that Forms Five Hydrogen Bonds to Guanosine: Guanidino G-Clamp

**Keywords:** antisense • DNA structures • hydrogen bonds • molecular recognition • X-ray crystallography

*Angew. Chem.* **2002**, *114*, 123–125



**The relative position of the Asp and Trp residues** in a peptide chain is important for recognizing a tetra-guanidinium receptor through hydrogen bonding and cation– $\pi$  interactions. The molecule not only binds with high affinity ( $K_a = 1.1 \times 10^8 \text{ M}^{-1}$ ), it also stabilizes the helical conformation of the peptide (see schematic representation) as demonstrated by NMR and CD spectroscopy.



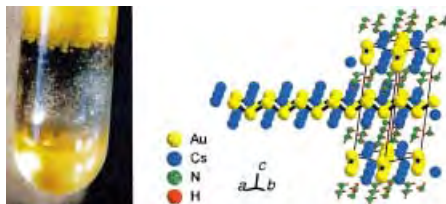
B. P. Orner, X. Salvatella, J. Sánchez Quesada, J. de Mendoza, E. Giralt, A. D. Hamilton\* .... 117–119

De Novo Protein Surface Design: Use of Cation– $\pi$  Interactions to Enhance Binding between an  $\alpha$ -Helical Peptide and a Cationic Molecule in 50 % Aqueous Solution

**Keywords:** helical structures • host–guest systems • molecular recognition • NMR spectroscopy • noncovalent interactions

*Angew. Chem.* **2002**, *114*, 125–127

**Treating CsAu with liquid  $\text{NH}_3$**  yields the deep blue ammoniate  $\text{CsAu} \cdot \text{NH}_3$  (see picture and structure). The unusual electronic structure, as well as the properties, indicate that this unique compound, which behaves like an alkali metal when dissolved in ammonia, may serve as a guide to a more thorough understanding of solvated electrons.



A.-V. Mudring, M. Jansen,\* J. Daniels, S. Krämer, M. Mehring, J. P. Prates Ramalho, A. H. Romero, M. Parrinello ..... 120–124

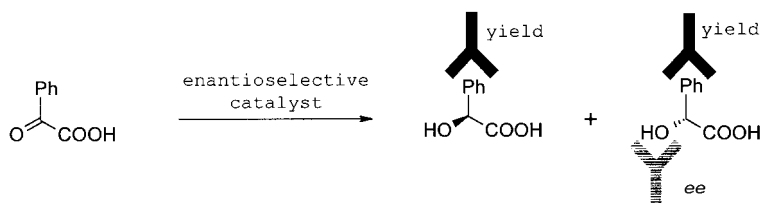
Cesiumauride Ammonia (1/1),  $\text{CsAu} \cdot \text{NH}_3$ : A Crystalline Analogue to Alkali Metals Dissolved in Ammonia?

**Keywords:** ammonia • cesium • gold • solvated electrons

*Angew. Chem.* **2002**, *114*, 128–132



**More than 1000** yields and *ee* determinations are possible per day using an immunoassay. This highly efficient screening method is based on the remarkable binding specificity of antibodies. It has been employed in the development of straightforward procedures for the direct conversion of  $\alpha$ -keto acids into chiral  $\alpha$ -hydroxy acids, for which the enantioselective reduction of benzoyl formic acid to mandelic acid serves as a model reaction (see scheme).



F. Taran, C. Gauchet, B. Mohar, S. Meunier, A. Valleix, P. Y. Renard, C. Créminon, J. Grassi, A. Wagner,\* C. Mioskowski\* ..... 124–127

High-Throughput Screening of Enantioselective Catalysts by Immunoassay

**Keywords:** antibodies • asymmetric catalysis • combinatorial chemistry • high-throughput screening • reduction

*Angew. Chem.* **2002**, *114*, 132–135



**Peptide length** affects the size of the ridges observed in the atomic force microscopy (AFM) images of the Langmuir–Blodgett films of amphiphilic peptides: Well-ordered LB films can be prepared from a 14-residue amphiphilic peptide (left), while ordered LB films with a wider lattice (right) are obtained from an 18-residue peptide. The  $100\text{ nm} \times 100\text{ nm}$  images pictured were obtained by AFM using carbon nanotube tips.



E. T. Powers, S. I. Yang, C. M. Lieber,\*  
J. W. Kelly\* ..... 127–130

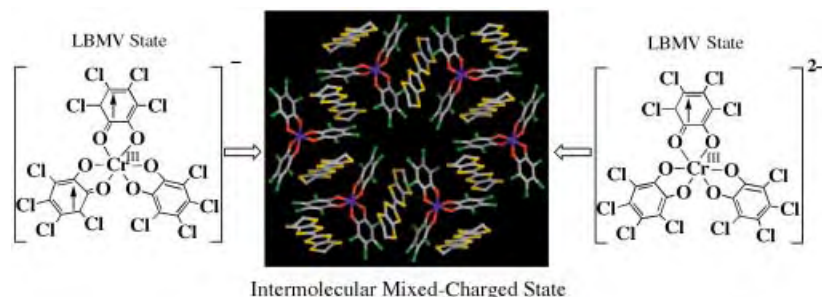
Ordered Langmuir–Blodgett Films of  
Amphiphilic  $\beta$ -Hairpin Peptides Imaged  
by Atomic Force Microscopy

**Keywords:** nanostructures • peptides •  
scanning probe microscopy •  
self-assembly • thin films

*Angew. Chem.* **2002**, *114*, 135–138



**Coexistence of two kinds of ligand-based mixed-valence (LBMV) isomers** is observed for the first time in the title compound (see scheme). Together with its mixed-charged state, the compound shows semiconducting behavior with an intermolecular ferromagnetic interaction, which is attributable to the association of five paramagnetic components in the crystal phase.



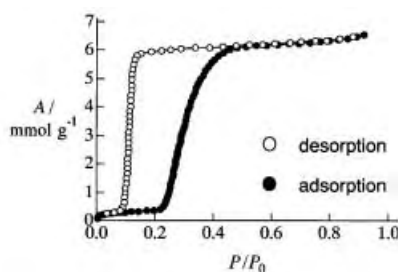
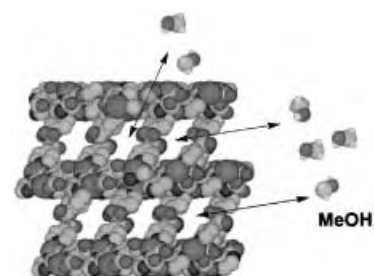
H.-C. Chang, S. Kitagawa\* .... 130–133

An Unprecedented Mixed-Charged State  
in a Supramolecular Assembly of Ligand-  
Based Mixed-Valence Redox  
Isomers  $(\text{ET}^+)_3[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_2^-$   
 $(\text{Cl}_4\text{Cat})^-][\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})(\text{Cl}_4\text{Cat})_2]^{2-}$

**Keywords:** chromium • donor–acceptor  
systems • magnetic properties • mixed-  
valent compounds • O ligands

*Angew. Chem.* **2002**, *114*, 138–141

**A hysteretic adsorption and desorption profile** (right) accompanied by a transformation of the crystal structure is observed for the title coordination polymer, which possesses a pillared-layer structure (left), on exposure to  $\text{H}_2\text{O}$  or MeOH vapor under pressure.



R. Kitaura, K. Fujimoto, S.-i. Noro,  
M. Kondo, S. Kitagawa\* ..... 133–135

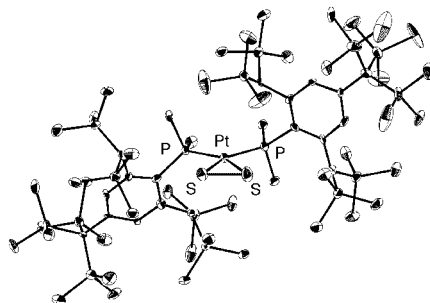
A Pillared-Layer Coordination Polymer  
Network Displaying Hysteretic Sorption:  
 $[\text{Cu}_2(\text{pzdc})_2(\text{dpyg})]_n$  (pzdc = Pyrazine-  
2,3-dicarboxylate; dpyg = 1,2-Di-  
(4-pyridyl)glycol)

**Keywords:** copper • crystal engineering •  
host–guest systems • hydrogen bonds •  
inclusion compounds • microporosity

*Angew. Chem.* **2002**, *114*, 141–143



**Rings with platinum:** The first platinum disulfur and diselenium complexes have been synthesized by taking advantage of new phosphane ligands bearing an extremely bulky substituent (see structure). The molecular structures of the disulfur and diselenium complexes are very similar, and these complexes, as well as an analogous dioxygen complex  $[(\text{PPh}_3)_2\text{PtO}_2]$ , have a square-planar geometry and a three-membered  $\text{PtE}_2$  ( $\text{E} = \text{S}, \text{Se}$ ) ring.



K. Nagata, N. Takeda,  
N. Tokitoh\* ..... 136–138

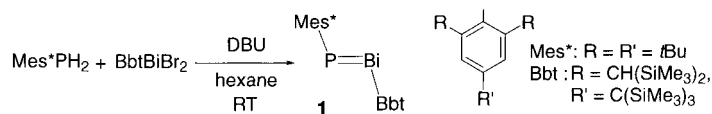
The First Disulfur and Diselenium  
Complexes of Platinum: Syntheses and  
Crystal Structures

**Keywords:** metallacycles • platinum •  
P ligands • selenium • sulfur

*Angew. Chem.* **2002**, *114*, 144–146



**The exceedingly different size of p orbitals is overcome** in the novel doubly bonded system between phosphorus and bismuth atoms that occurs in the first stable phosphabismuthene **1**. Compound **1** was obtained from the condensation reaction of Mes\*PH<sub>2</sub> with an overcrowded dibromobismuthane by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (see scheme).



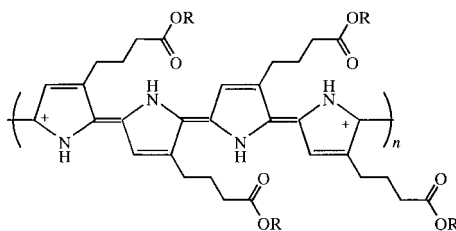
*Angew. Chem.* **2002**, *114*, 147–149

T. Sasamori, N. Takeda, M. Fujio,  
M. Kimura, S. Nagase,  
N. Tokitoh\* ..... 139–141

Synthesis and Structure of the First Stable  
Phosphabismuthene

**Keywords:** bismuth • multiple bonds •  
phosphorus

**Conducting films and pellets** formed from  $\beta$ -substituted polypyrroles (see picture; R = H, CH<sub>3</sub>) erode under aqueous conditions in a pH-dependent manner, which allows erosion rates to be tailored through differences in polymer side-chain structure. These conducting materials support the attachment, proliferation, and differentiation of primary human cells, and could lead to the use of conducting polymers in a variety of new biomedical applications.



*Angew. Chem.* **2002**, *114*, 149–152

A. N. Zelikin, D. M. Lynn, J. Farhadi,  
I. Martin, V. Shastri,\*  
R. Langer\* ..... 141–144

Erodible Conducting Polymers for  
Potential Biomedical Applications

**Keywords:** biomaterials • cell  
differentiation • conducting materials •  
polymers • polypyrroles

**Methyldiyne, vinylidene, and ethyldiyne on a surface:** Inelastic neutron scattering (INS) vibrational spectroscopy is used to investigate the surface intermediate species formed during the decomposition of methane on Ru/Al<sub>2</sub>O<sub>3</sub> and Ni/SiO<sub>2</sub> catalysts. The findings are compared to previous work on idealized single-crystal model catalysts and begin to bridge the gap between surface science and real-world catalysts in terms of the type of material and pressure used.

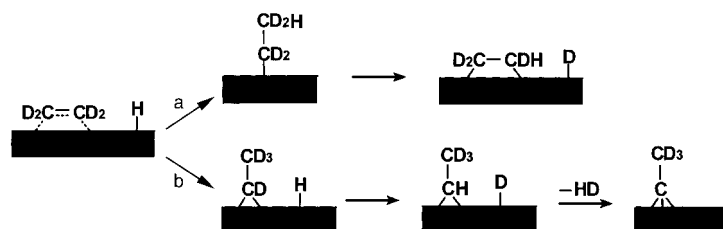
S. Chinta, T. V. Choudhary,  
L. L. Daemen, J. Eckert,  
D. W. Goodman\* ..... 144–146

Characterization of C<sub>2</sub> (C<sub>2</sub>H<sub>y</sub>)  
Intermediates from Adsorption and  
Decomposition of Methane on Supported  
Metal Catalysts by in situ INS Vibrational  
Spectroscopy

**Keywords:** heterogeneous catalysis •  
methane • nickel • reaction  
mechanisms • ruthenium • surface  
analysis

*Angew. Chem.* **2002**, *114*, 152–154

**Ethylene on a surface:** C<sub>2</sub>D<sub>4-x</sub>H<sub>x</sub> (x = 0–4) species that result from H/D exchange reactions on a Pt(111) surface are quantitatively identified by using a Cs<sup>+</sup> reactive ion scattering method (RIS). Two temperature-dependent pathways are identified for the exchange process (see scheme; a: T < 265 K; b: T > 265 K).



*Angew. Chem.* **2002**, *114*, 154–156

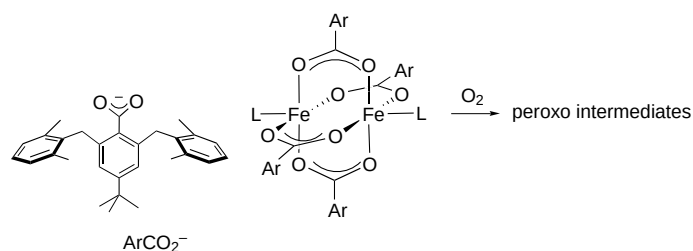
C. M. Kim,\* C.-H. Hwang, C.-W. Lee,  
H. Kang\* ..... 146–148

Real-time Observation of the H/D  
Exchange Reaction between Ethylene  
and Hydrogen on Pt(111)

**Keywords:** H/D exchange •  
heterogeneous catalysis • platinum •  
reaction mechanisms • surface analysis



**The structural influences of the supporting carboxylate ligand** on biologically relevant Fe/O<sub>2</sub> chemistry are emphasized by the unusual Raman and Mössbauer spectroscopic properties of the intermediate derived from **1** relative to those of known (peroxo)diferrous species. These (peroxo)diferrous intermediates were generated from paddlewheel complexes (L = py, MeIm, and thf) of the new carboxylate ArCO<sub>2</sub><sup>−</sup> ligand on reaction with O<sub>2</sub>. MeIm = 1-methylimidazole, py = pyridine.



*Angew. Chem.* **2002**, *114*, 157–160

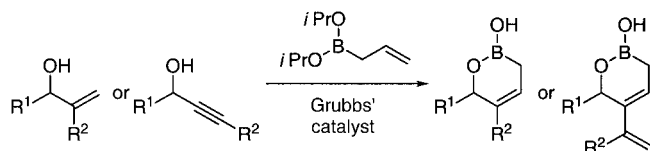
F. A. Chavez, R. Y. N. Ho, M. Pink,  
V. G. Young, Jr., S. V. Kryatov,  
E. V. Rybak-Akimova,\* H. Andres,  
E. Münck,\* L. Que, Jr.,\*  
W. B. Tolman\* ..... 149–152

Unusual Peroxo Intermediates in the  
Reaction of Dioxygen with Carboxylate-  
Bridged Diiron(II,II) Paddlewheel  
Complexes

**Keywords:** bioinorganic chemistry •  
carboxylate ligands • iron • oxygen



**In only one to four steps**, complex structures containing multiple rings, stereo-centers, and unsaturated units have been prepared by employing a new annulation reaction of unsaturated boronic esters with allylic and propargylic alcohols (see scheme).



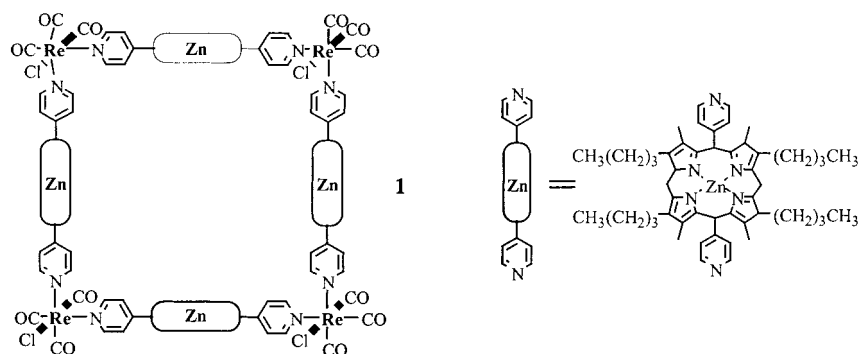
*Angew. Chem.* **2002**, *114*, 160–162

G. C. Micalizio,  
S. L. Schreiber\* ..... 152–154

A Boronic Ester Annulation Strategy for  
Diversity-Oriented Organic Synthesis

**Keywords:** annulation • boronic esters •  
diversity-oriented synthesis •  
domino reactions • metathesis

**Micropatterned thin films** of tailorable molecular materials with uniform, nanoscale cavities, such as **1**, were prepared by soft lithographic methods. In this form the materials readily diffract visible light, and because the efficiency of diffraction is enhanced by sorption of guest molecules, the diffraction response can be used for signal transduction in chemical-sensing applications.



*Angew. Chem.* **2002**, *114*, 162–165

G. A. Mines, B.-C. Tzeng,  
K. J. Stevenson, J. Li,  
J. T. Hupp\* ..... 154–157

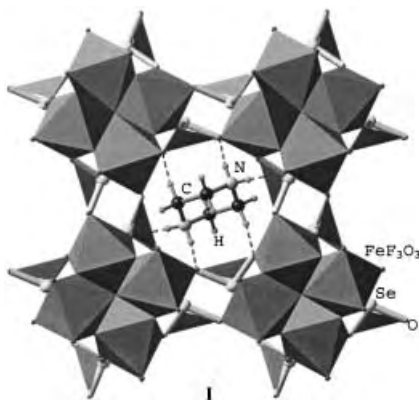
Microporous Supramolecular  
Coordination Compounds as  
Chemosensory Photonic Lattices

**Keywords:** microporous materials •  
patterning • sensors • supramolecular  
chemistry • thin films



**One dimensional channels** are formed in the three-dimensional open-framework iron selenite  $[\text{C}_4\text{N}_2\text{H}_{12}]_{0.5}[\text{Fe}_2\text{F}_3(\text{SeO}_3)_2]$  (**1**), which was synthesized hydrothermally from  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , HF, and  $\text{SeO}_2$  in the presence of the organic amine piperazine. The same inorganic framework was also obtained with the amines diethylenetetramine, 1,3-diaminopropane, and ethylenediamine. Compound **1** displays unusual magnetic frustration behavior that is attributed to the tetrahedral geometry.

*Angew. Chem.* **2002**, *114*, 166–169

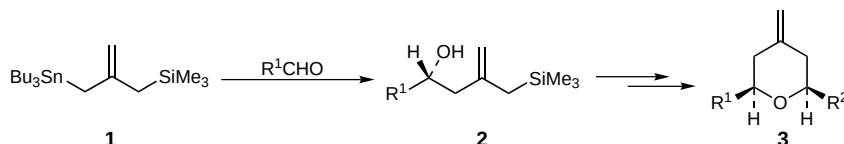


A. Choudhury, U. Kumar D,  
C. N. R. Rao\* ..... 158–161

Three-Dimensional Organically  
Templated Open-Framework Transition  
Metal Selenites

**Keywords:** crystal growth • iron •  
magnetic properties • mesoporous  
materials • selenium

**Useful tetrahydropyran units** such as **3** can be prepared with high diastereoselectivity (d.r. > 30:1). A key step is the catalytic asymmetric allyl-transfer reaction from **1** to achiral aldehydes catalyzed by  $[(R)\text{-binol}]\text{Ti}^{\text{IV}}\{\text{OCH}(\text{CF}_3)_2\}_2$  to give **2** (90–97% *ee*). A second allyl-transfer reaction from **2** to a carbonyl compound leads to **3**. binol = 2,2'-binaphthol.



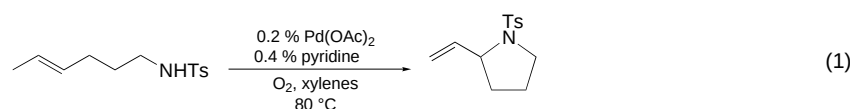
*Angew. Chem.* **2002**, *114*, 169–171

C.-M. Yu,\* J.-Y. Lee, B. So,  
J. Hong ..... 161–163

Sequential Catalytic Asymmetric Allylic  
Transfer Reaction: Enantioselective and  
Diastereoselective Construction of  
Tetrahydropyran Units

**Keywords:** aldehydes • asymmetric  
catalysis • chirality • Lewis acids •  
titanium

**Facile and efficient:** a palladium-catalyzed intramolecular oxidative amination reaction [Eq. (1)] that uses molecular oxygen as a stoichiometric oxidant. These reactions require no cocatalyst for efficient reoxidation of the palladium, they operate in solvents ranging from heptane to dimethylsulfoxide, and achieve up to 250 turnovers (TO) and rates of 70  $\text{TO h}^{-1}$ .



*Angew. Chem.* **2002**, *114*, 172–174

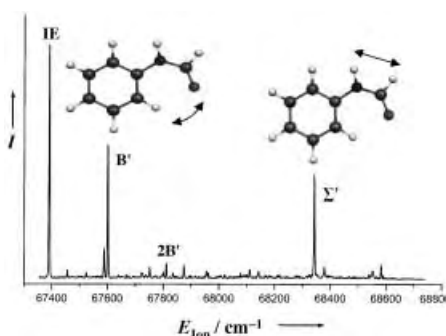
S. R. Fix, J. L. Brice,  
S. S. Stahl\* ..... 164–166

Efficient Intramolecular Oxidative  
Amination of Olefins through Direct  
Dioxygen-Coupled Palladium Catalysis

**Keywords:** amination • homogeneous  
catalysis • oxidation • palladium •  
synthetic methods

**Spectroscopic characterization of cationic amides:** ZEKE photoelectron spectroscopy has been successfully applied to isomers of the model peptide formanilide. The spectra indicate that significant charge delocalization occurs from the aromatic ring to the side chain in the ion. The picture shows the spectrum of the *trans* isomer together with the side-chain in-plane bending and amide stretching modes that are associated with the  $B'$  and  $\Sigma'$  bands. IE = ionization energy.

*Angew. Chem.* **2002**, *114*, 174–176



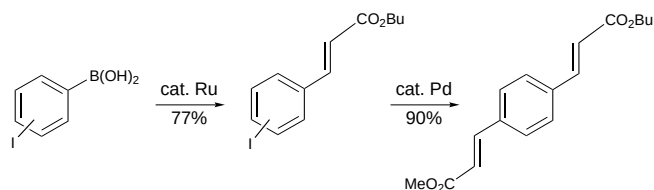
S. Ullrich, G. Tarczay, X. Tong,  
C. E. H. Dessent,  
K. Müller-Dethlefs\* ..... 166–168

ZEKE Photoelectron Spectroscopy of the  
*cis* and *trans* Isomers of Formanilide

**Keywords:** amides • cations •  
laser spectroscopy • photoelectron  
spectroscopy • ZEKE spectroscopy

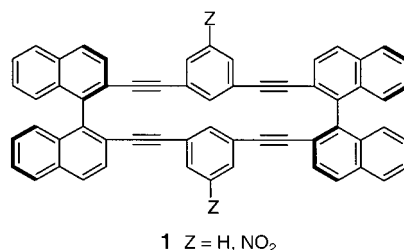


**Aryl boronic acids can undergo a Heck-type reaction** catalyzed by  $\text{Ru}^{\text{II}}$  in the presence of  $\text{Cu}^{\text{II}}$ , which serves as a reoxidant in each cycle (see scheme, step 1). Compatibility with halide substituents offers attractive synthetic potential (step 2).



*Angew. Chem.* **2002**, *114*, 177–179

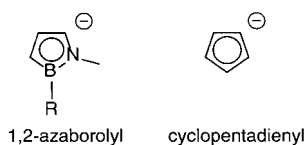
The “commercially available chirality” of the binaphthyl units and the efficiency of the coupling reactions were crucial to the synthesis of double-helical alkynyl cyclophanes **1** in enantiopure form. The unique properties of these molecules have been unambiguously confirmed by single-crystal X-ray structure analysis and CD spectroscopy.



*Angew. Chem.* **2002**, *114*, 179–181

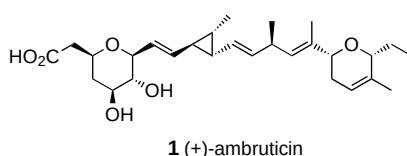


The substituent on boron allows the electronic nature of the heterocycle of *B*-heteroatom-substituted ( $\text{R} = \text{H}, \text{O}, \text{S}, \text{N}, \text{P}$ , and  $\text{F}$ ) 1,2-azaborolyl complexes to be modulated. Given that 1,2-azaborolyl is isoelectronic with cyclopentadienyl (see scheme), one of the most widely used ligands in organometallic chemistry, it seems likely that the diverse array of compounds synthesized in this study will stimulate the development of applications of  $\eta^5$ -(1,2-azaborolyl) ligands in metal-catalyzed processes.



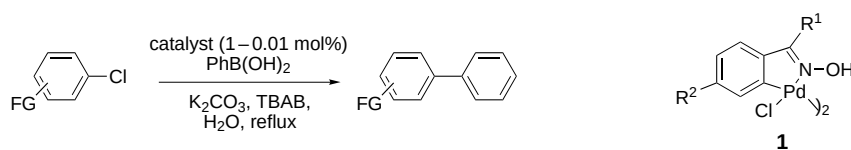
*Angew. Chem.* **2002**, *114*, 182–184

**Highly stereoselective radical cyclization** and olefin metathesis reactions for the construction of oxacyclic building blocks were key steps in the convergent total synthesis of the orally active antifungal agent ambruticin (**1**).



*Angew. Chem.* **2002**, *114*, 184–186

**Refluxing water is a good solvent** for the coupling reactions of aryl and heteroaryl chlorides with phenylboronic acid (see scheme; FG = functional group). The reactions use oxime-derived palladacycles **1** as thermally stable catalysts, potassium carbonate as base, and tetrabutylammonium bromide (TBAB), and can be carried out in the presence of air.



*Angew. Chem.* **2002**, *114*, 187–189

E. J. Farrington, J. M. Brown,\*  
C. F. J. Barnard, E. Rowsell ... 169–171

Ruthenium-Catalyzed Oxidative Heck Reactions

**Keywords:** boronic acids • Heck reaction • palladium • ruthenium • synthetic methods

D. L. An, T. Nakano, A. Orita,  
J. Otera \* ..... 171–173

Enantiopure Double-Helical Alkynyl Cyclophanes

**Keywords:** alkynes • chirality • circular dichroism • cyclophanes • helical structures

S.-Y. Liu, M. M.-C. Lo,\*  
G. C. Fu \* ..... 174–176

1,2-Azaborolyls, Isoelectronic Analogues of the Ubiquitous Cyclopentadienyl Ligand: Synthesis of *B*-Heteroatom-Substituted 1,2-Azaborolyl Complexes and an Assessment of Their Electronic Features

**Keywords:** boron • cyclopentadienyl ligands • heterocycles • N ligands

E. Lee,\* S. J. Choi, H. Kim, H. O. Han,  
Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim,  
W. S. Jang ..... 176–178

Total Synthesis of Ambruticin

**Keywords:** antifungal agents • metathesis • natural products • radical reactions • total synthesis

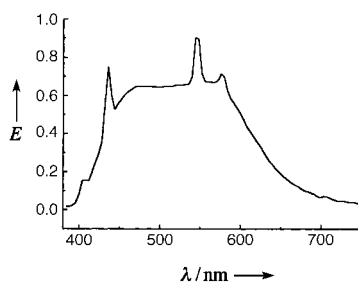
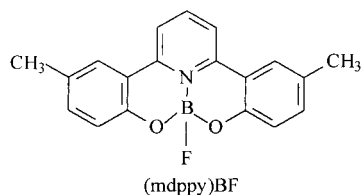
L. Botella, C. Nájera \* ..... 179–181

A Convenient Oxime-Carbapalladacycle-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides in Water

**Keywords:** biaryls • C–C-coupling • cross-coupling • palladium • phase-transfer catalysis



**Electroluminescence from 400 to 700 nm** (see right picture) is exhibited by an organic electroluminescent device based on (mdppy)BF (left picture) as emitter and a 1,1'-biphenyl-4,4'-diamine derivative as a hole-transporting material. The device emits white light with high efficiency and good color purity.



*Angew. Chem.* **2002**, *114*, 190–192

Y. Liu, J. Guo, H. Zhang,  
Y. Wang\* ..... 182–184

Highly Efficient White Organic  
Electroluminescence from a Double-  
Layer Device Based on a Boron  
Hydroxyphenylpyridine Complex

**Keywords:** boron • electroluminescence •  
luminescence • thin films



Supporting information on the WWW  
(see article for access details).

\* Author to whom correspondence should be addressed

The cover picture was generated by Thomas Ward and Christophe Thomas with the Pov-Ray program.



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<http://www.angewandte.com>

**M. Nevalainen and A. M. P. Koskinen** wish to point out that in their Communication in Issue 21, pp. 4060–4062, only compound **1** and not **2** is a naturally occurring sesquiterpene. Furthermore, **2** should not be named as a germacradiene derivative but as a norgermacradiene derivative, because of the missing methyl group.

In the Communication of **Y. Tobe et al.** in Issue 21, pp. 4072–4074, trace g is missing from Figure 1, a mistake for which the editorial team apologizes. The correct figure is shown below. In addition, the authors wish to point out that the fullerene structure of  $C_{20}$  is purely speculative and has to date not been proven.

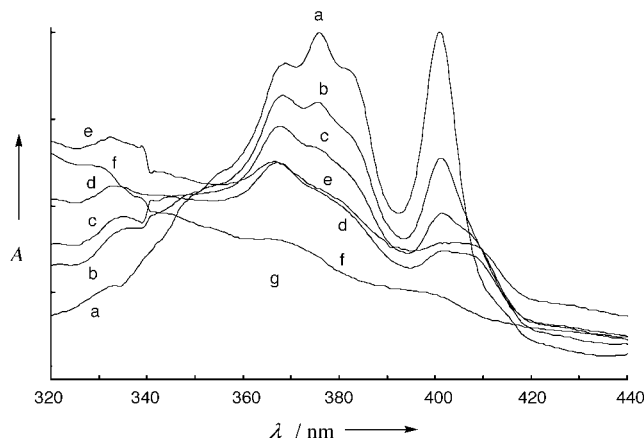
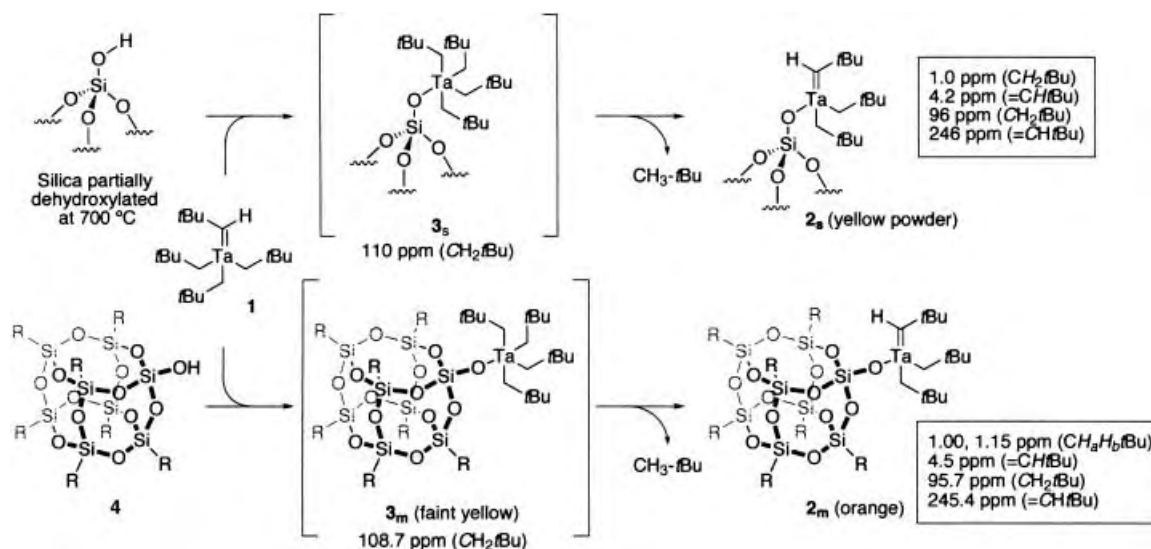


Figure 1. UV/Vis spectral changes for **1a** in a 2-methyltetrahydrofuran/ethanol (6:1) matrix at 77 K by irradiation with a low-pressure mercury lamp. a) before irradiation; b–e) after irradiation for 1, 3, 13, and 24 h, respectively; f) after irradiation for 24 h followed by thaw and refreeze; g) subtraction of line f from line e.

In the Communication of **K. Hegetschweiler and co-workers** in Issue 22, pp. 4179–4182, two important relevant papers were not quoted, for which the authors apologize: R. Schwesinger, K. Piontek, W. Littke, O. Schweikert, H. Prinzbach, C. Krüger, Y.-H. Tsay, *Tetrahedron Lett.* **1982**, 23, 2427–2430; b) R. Schwesinger, K. Piontek, W. Littke, H. Prinzbach, *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 318–319. The authors apologize for this omission. In particular, ref. a describes complex formation of  $Ba^{2+}$  with *cis*-benzenetrioxide, a tridentate, tripodal oxygen donor. The resulting complex has icosahedral structures with approximate *T* symmetry, analogous to the complex described by Hegetschweiler and co-workers. Unfortunately, crystallographic data of this Ba complex are not available in the database of the Cambridge Crystallographic Data Centre. The authors thank Professor Prinzbach, Freiburg, for his advice.

In the Communication of **C. Copéret, J.-M. Basset, and L. Emsley et al.** in Issue 23, 2001, pp. 4493–4496, a printing error caused the inadvertent omission of some parts of the structures in Scheme 1. The correct scheme is shown below. The editorial team apologizes for this error.



Scheme 1. Comparison of the reaction of silica partially dehydroxylated at 700 °C ( $SiO_{2(700)}$ ) versus  $(c-C_5H_9)_7Si_7O_{12}SiOH$ .

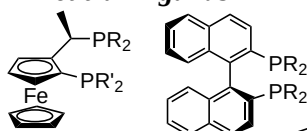
### Metals

Sc, Ti, V, Cr, Mo, Ru, Os,  
Co, Rh, Ir, Ni, Pd, Pt, Cu, Zn

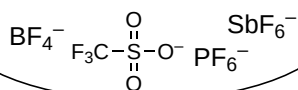
### Additives

$R_4N^+X^-$ ,  $PR_3$ ,  $NR_3$ ,  
 $R_3P=O$ ,  $RO^-M^+$

### Neutral Ligands



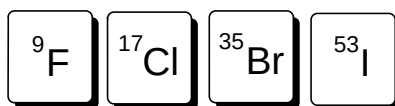
### Counter Ions



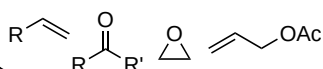
### Solvent

$Et_2O$ , THF, DMF,  $CH_2Cl_2$ ,  
Toluene, Dioxane,  $H_2O$

### Halide Ligands



### Reactants

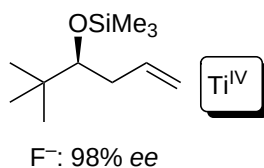
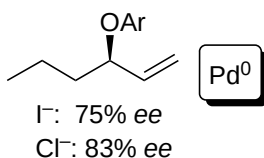
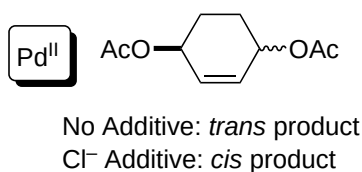
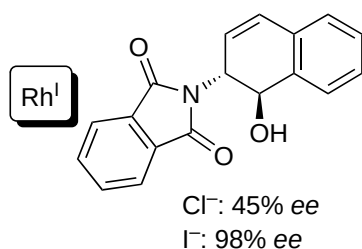
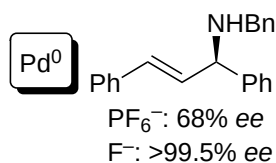


### Temperature

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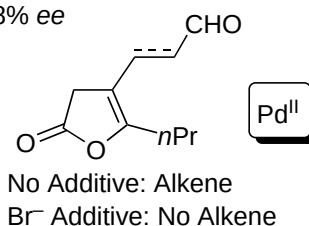
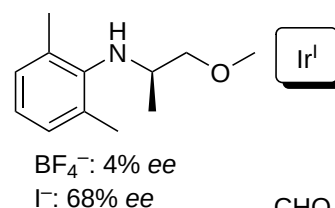
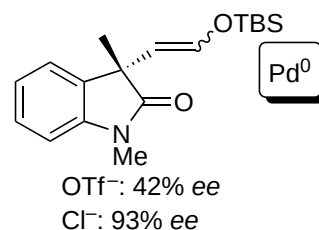
Optimization  
Variables

Halide  
Effects



Optimization  
Variables

Halide  
Effects



Halide effects have been discovered in many transition metal catalyzed processes and have become an important aspect of catalyst optimization.

# Halide Effects in Transition Metal Catalysis

Keith Fagnou and Mark Lautens\*

*Dedicated to Professors B.M. Trost and D.A. Evans on the occasion of their 60th birthdays*

Among the most common ligands found on transition metal catalysts are halide ions. Of the commercially available catalysts or pre-catalysts, most are halo-metal complexes. In recent years, manipulation of this metal-halide functionality has revealed that this can be used as a highly valuable method of tuning the reactivity of the complex. Variation of the halide ligand will usually not alter the nature of the system to the extent that it becomes unreactive but will impart sufficiently large changes that differences in reactivity or selectivity occur.

These differences are a product of the steric and electronic properties of the halide ligand which has the ability to donate electron density to the metal occurs in a predictable manner. Despite the common perception in asymmetric catalysis that halide ligands are of secondary importance compared to chiral ligands, halide ligands have been found to exert dramatic effects on the enantioselectivity of asymmetric transformations. While the mechanism of action is known for relatively few of the cases, many intriguing and potentially synthetically useful trends are

apparent. This review discusses the physical properties of the halides and their effects on stoichiometric and catalytic transition metal processes. The metal-halide moiety thus emerges as a tunable functionality on the transition metal catalyst that can be used in the development of new catalytic systems.

**Keywords:** asymmetric synthesis • halogens • homogeneous catalysis • ligand effects • transition metals

## 1. Introduction

The important role of spectator or ancillary ligands in transition metal ligand-substitution reactions has long been recognized. Through judicious choice of the ancillary ligands, it is often possible to alter the steric and electronic properties of the metal and therefore influence the course of many transition metal processes. Within the field of transition metal catalysis, catalysts containing halide ligands are ubiquitous, a result of the stability of the metal-halide bond. Despite the prevalence of this functionality, a full appreciation of its utility in catalyst development has only recently become widespread. As ancillary ligands, halides can provide an invaluable handle with which the reactivity and selectivity of a catalyst can be fine-tuned for a given transformation.

In asymmetric catalysis, attention is primarily paid to the choice of metal and chiral ligand, this is because of the

inherent difficulty in selecting a chiral ligand that will give high enantioselectivities. For this reason, halide ligands within the coordination sphere are often regarded as being of limited importance. In fact, most discussions of halide ligands involve their removal from the coordination sphere and replacement with weakly coordinating anions such as triflate, hexafluorophosphate, and hexafluoroantimonate.<sup>[1]</sup> Investigations into the role of halide spectator ligands are far less frequent. When these reports are brought together, intriguing trends appear which could prove useful in the development of new catalytic asymmetric transformations.

The body of this review has been divided into three sections. In the first section, emphasis is placed on understanding how the physical properties of the halides will influence the behavior of the metal complex as a whole. The second section deals with stoichiometric transformations involving transition metal halide complexes where the halide has been found to influence the reactivity of the system. By learning how halide ligands can influence stoichiometric transformations, a better understanding of halide effects in catalytic transformations can be gained. Catalytic processes that involve halide effects are presented in the third section. Emphasis in this section is placed on the experimental evidence for halide effects and selected asymmetric catalytic transformations are presented

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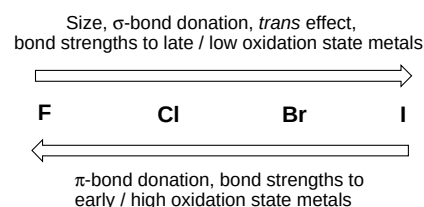
first. Understanding the influence of ancillary ligands on the enantioselectivity can be a challenging issue since it is often very difficult to pinpoint the precise enantiodiscriminating step in many catalytic processes. Despite this limitation, several reactions have appeared where the halide has been found to dramatically affect the enantioselectivity of the transformation. Halide effects have also been observed in achiral catalytic transformations. Since the mechanisms of several achiral processes are known, it is often possible to deduce how the halide ligand is influencing the transformation.

The chemistry of salt effects in organic and organometallic chemistry has been previously described in an excellent review which can serve as a starting point for the material covered herein.<sup>[2]</sup> This review will focus predominantly on the work that has appeared since 1992 that deals with the effect of changing the nature of the halide ligand on a transition metal complex. The effect of changing the nature of the “non-coordinating” ligands of cationic complexes will not be addressed.<sup>[3]</sup>

## 2. Understanding Halide Effects

### 2.1. Properties of Halide Ligands

The most important properties of the halide ligands include: 1) steric properties, 2) electronic properties ( $\sigma$  and  $\pi$  bonding), 3) polarizability, 4) nucleophilicity, and 5) the *trans* effect. The trends of these properties are outlined in Scheme 1.



Scheme 1. Trends in the properties of halide ligands.

### 2.2. Steric Properties of the Halides

The relative size of the halide ligand can play a decisive role in reactions where the halide is *cis* to the reaction site or on metal complexes with high coordination numbers. For example, as the steric bulk of a ligand increases, oxidative addition processes can be slowed while reductive elimination may be favored as a means of reducing the steric interactions. The steric bulk of halide ligands increases down the group in terms of ionic radii, covalent radii,<sup>[4]</sup> and cone angle<sup>[5]</sup> (Table 1).

Table 1. Steric properties of the halides.

|                     | F     | Cl    | Br    | I     |
|---------------------|-------|-------|-------|-------|
| Ionic Radius [Å]    | 1.36  | 1.81  | 1.95  | 2.16  |
| Covalent Radius [Å] | 0.709 | 0.994 | 1.142 | 1.333 |
| Cone Angle [°]      | 92    | 102   | 105   | 107   |

### 2.3. Electronic Properties: $\sigma$ and $\pi$ Bonding

Predicting the nature of the interactions between a halide ligand and a transition metal is a complicated issue because

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Keith Fagnou was born in Saskatoon, Saskatchewan Canada in 1971. He received his bachelors degree in education with distinction (B.Ed.) from the University of Saskatchewan in 1995, and after teaching for one year continued his studies at the University of Toronto. In 1998, he joined the research group of Prof. Mark Lautens working in the area of transition metal catalysis. In 2000 he received his M.Sc. and is currently conducting Ph.D. studies in the same area.



M. Lautens



K. Fagnou

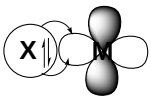
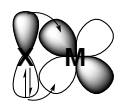
these interactions rely not only on the nature of the halide ligand, but also on several properties of the transition metal complex, including:

1. the transition metal and its oxidation state (number of d electrons)
2. the coordination number and geometry
3. the nature of the other ligands within the coordination sphere.

These factors are interrelated since a change in one can affect the others. They must therefore be regarded globally when considering the nature of the interactions of a halide ligand.

### 2.3.1. The Nature of the Halide Ligand

It is generally appreciated that the electronegativities of the halogens increase up the group, with fluorine being the most electronegative element. As a consequence of the halide electronegativities and the availability of their s electrons, the ability to form  $\sigma$  bonds increases down the group (Scheme 2). In the absence of other interactions between the halide and

|    | Electronegativity |                                                                                   |                                         |
|----|-------------------|-----------------------------------------------------------------------------------|-----------------------------------------|
| F  | 3.98              |  | $\sigma$ donation:<br>$F < Cl < Br < I$ |
| Cl | 3.16              |  | $\pi$ donation:<br>$F > Cl > Br > I$    |
| Br | 2.96              |                                                                                   |                                         |
| I  | 2.66              |                                                                                   |                                         |

Scheme 2. Electronic properties of halide ligands.

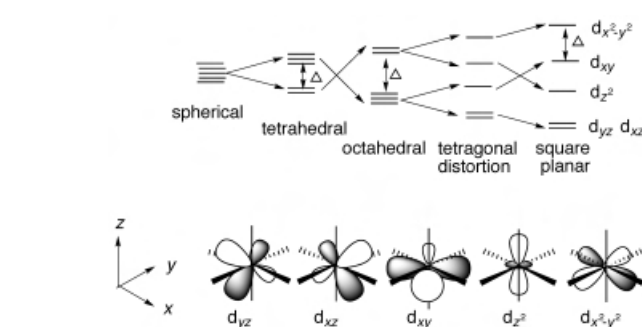
the metal, iodide would be expected to form the strongest bonds and donate the most electron density to the metal by these  $\sigma$  interactions. This is rarely the case, however, since  $\pi$  interactions commonly occur between the halide lone-pair electrons and the metal d orbitals.<sup>[6]</sup> When  $\pi$  interactions predominate, the opposite trend in electron donation to that predicted by electronegativity can be observed, and fluorine is the strongest  $\pi$  donor.<sup>[7]</sup>

### 2.3.2. Effect of the Transition Metal Complex on $\pi$ Bonding

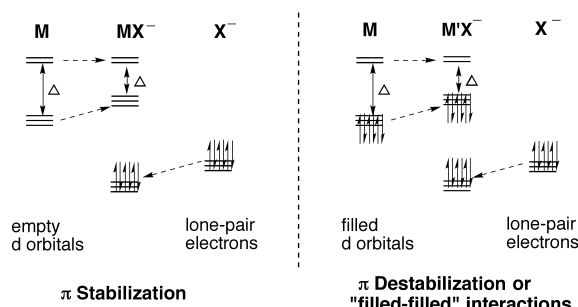
For  $\pi$  interactions to be possible with transition metals, a metal orbital of appropriate symmetry must be available to interact with the halide lone pairs. The d orbital degeneracies and relative energies will be affected by the coordination geometry of the complex and can be predicted by the ligand-field model (Scheme 3).

The ways  $\pi$  bonding will influence the reactivity of a complex can be revealed by determining whether the  $\pi$  donation will have a stabilizing or destabilizing effect. The number of d electrons on the metal center must be considered and if there is an empty d orbital of suitable geometry a net stabilization can result. If the d orbital is fully occupied, a net destabilization termed “filled–filled” interactions will occur (Scheme 4).<sup>[6]</sup> As the d electron count increases from  $d^0$  to  $d_{LS}^6$ , (LS = low spin) the effects of  $\pi$  donation will become more destabilizing in nature.

While it may be anticipated that square-planar 16-electron  $d^8$  complexes would possess significant  $\pi$  bonding to stabilize



Scheme 3. Ligand-field splitting for common coordination geometries.



Scheme 4.  $\pi$  Stabilization and destabilization arising from molecular-orbital interactions for an octahedral coordination geometry.

the low electron count, this is not the case; the only empty d orbital,  $d_{x^2-y^2}$ , does not possess the appropriate symmetry to allow overlap with the halide ligand lone-pair electrons. The only orbitals with appropriate geometry,  $d_{yz}$ ,  $d_{xz}$ , and  $d_{xy}$ , are filled and any interactions between these orbitals and the halide lone-pair orbitals will be destabilizing in nature.

When a  $\pi$ -acid ligand is coordinated to a square-planar 16-electron  $d^8$  complex, however, some  $\pi$  donation will be observed. This is because the presence of strong  $\pi$  acids, such as carbonyl and nitrosyl ligands, can act to reduce the influence of filled–filled interactions through a “push–pull” mechanism. The CO ligand, for example, can accept electron density into its  $\pi^*$ -antibonding orbital which will reduce the electron density of the occupied metal d orbitals (“pull”) and therefore reduce the degree of filled–filled destabilization produced through halide ligand  $\pi$  donation (“push”). In  $d^8$  square-planar complexes this push–pull mechanism results in a reduction of electron density in the occupied  $d_{yz}$ ,  $d_{xz}$ , and  $d_{xy}$  orbitals and permits  $\pi$  donation when  $\pi$ -acid ligands are present. This explains, for example, why  $\pi$  donation from the halide ligands (X) is observed in Vaska-type complexes,  $[\text{Ir}(\text{PR}_3)(\text{CO})\text{X}]$ .

Consideration of the coordination geometry and the presence of  $\pi$  effects is relevant if an intermediate along the reaction pathway contains 14- or 16-electrons.<sup>[6]</sup> The donating ability of the halide ligand can stabilize coordinative unsaturation and low electron counts making this step in the process more favorable. The reverse is also true. For example, the addition of a sixth ligand to a 16-electron  $d^6$  complex to give an 18-electron octahedral product will be disfavored by the presence of strongly  $\pi$ -donating ligands, a result of unfavorable filled–filled interactions. These concepts are illustrated in Section 3.2.



## 2.4. Hard/Soft Interactions and Polarizability

As a general rule of thumb, it can be said that a *hard* species will prefer to bind other *hard* species and *soft* will bind *soft*. With regard to the halides, their relative polarizability or softness is expected to increase down the group.<sup>[8]</sup> The hard/soft character of the transition metals follows expected trends. A transition metal will become softer in character as its oxidation state is lowered, the further down the group it lies, and the further to the right in the transition metal series it is found. It can be expected that as a transition metal becomes softer in character it will increasingly prefer to bind the heavier halides. On the other hand, high-oxidation state hard metal centers will prefer to bind to ligands which can better donate electron density to the metal and so would prefer to bind fluoride. Experimental evidence supports these predictions.<sup>[9–11]</sup>

Evidence for the importance in considering these hard/soft interactions can be found in the relative formation constants for various  $M-X^{n+}$  species. From Table 2 it can be seen that

Table 2. Formation constants for hard and soft acids and bases.

|                  | F <sup>−</sup> | Cl <sup>−</sup> | Br <sup>−</sup> | I <sup>−</sup> |
|------------------|----------------|-----------------|-----------------|----------------|
| H <sup>+</sup>   | 3              | −7              | −9              | −9.5           |
| Zn <sup>2+</sup> | 0.7            | −0.2            | −0.6            | −1.3           |
| Cu <sup>2+</sup> | 1.2            | 0.05            | −0.03           | −              |
| Hg <sup>2+</sup> | 1.03           | 6.74            | 8.94            | 12.87          |

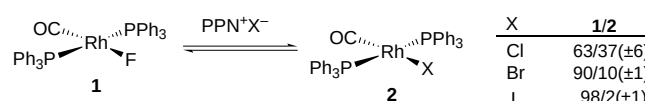
[a] Values are logarithms of equilibrium constant for  $[M_{(aq)}]^{n+} + X^- \rightleftharpoons [MX_{(aq)}]^{(n-1)+}$ .

H<sup>+</sup> and Zn<sup>II</sup> are hard in nature and will preferentially bind to fluoride. The Cu<sup>II</sup> center is a borderline case showing little variation among the halides, while the Hg<sup>II</sup> ion should be considered as soft since it binds strongest to iodide.<sup>[12]</sup> Further experimental evidence for these types of interactions lies in the relative rates of aquation for complexes of type  $[M(NH_3)_5X]^{2+}$  where  $M = Co^{III}$ ,  $Cr^{III}$ ,  $Ru^{III}$ ,  $Rh^{III}$ , and  $Ir^{III}$  (Table 3).<sup>[13]</sup> For the harder metals,  $Co^{III}$  and  $Cr^{III}$ , iodide is most easily displaced. The order is reversed for  $Rh^{III}$  and  $Ir^{III}$  where it is easier to displace the lighter halides. The  $Ru^{III}$  center is an intermediary case where there is no distinct trend. Thus, as one descends the group or moves right along a transition series, the soft character of the metal increases for a particular oxidation state.

The other ligands within the coordination sphere can also affect the hard/soft character of the metal. For example, with the  $[Co(CN)_5X]^{3-}$  ion, fluoride is the most easily displaced halide indicating that the metal is behaving as a soft base, in contrast to the situation found for the  $[Co(NH_3)_5X]^{2+}$  ion indicated above.<sup>[11]</sup> This example indicates that the CN ligands

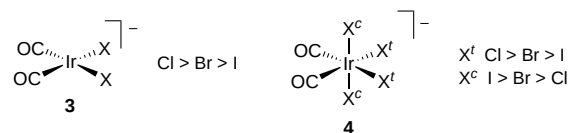
are able to impart a softer character to the Co center than are the hard  $NH_3$  ligands.

Further evidence for other ligands within the coordination sphere affecting the hard/soft character of the metal has been documented for metal–carbonyl compounds. For example, Forster and Hoffman showed that fluoride binds strongest to  $[Rh(CO)(PPh_3)_2]^+$  ions under aprotic conditions.<sup>[14]</sup> An illustrative set of experiments involves the treatment of the rhodium–fluoride complex **1** with an equivalent of bis(triphenylphosphane)nitrogen halide (PPNX) and determining the equilibrium ratio of rhodium halides **1** and **2** (Scheme 5). From these results it is evident that fluoride binds the strongest and iodide the weakest—opposite to what would be expected based on hard/soft arguments. This result can be rationalized by appreciating that push–pull interactions will occur between the halide and the *trans* CO ligand. Since these interactions will be maximal with the lighter halides, F will be most tightly bound.



Scheme 5. Effect of push–pull interactions on the hard/soft character of a transition metal complex.

Another example of ligands affecting the hard/soft character of the metal is found with halocarbonyliridate complexes **3** and **4** (Scheme 6).<sup>[14a]</sup> The influence of the *trans* CO ligands is again observed with **3** to which Cl is preferentially bound.



Scheme 6. Differential effect of push–pull interactions at *cis* and *trans* coordination sites.

Complex **4** is particularly illustrative, since the presence of the *cis* CO ligands results in halide coordination sites that differ dramatically in their hard/soft character. As with **1–3**, the CO ligands on **4** result in a “hardening” of the corresponding *trans* coordination sites  $X^t$ . Since the push–pull effect is highly directional, the positions *cis* to the CO ligands  $X^c$  retain their soft character. Thus, at positions  $X^t$ , *trans* to the CO ligands where the push–pull effect is greatest, chloride is preferentially bound. At positions  $X^c$ , where the electronic effect of the CO ligands is reduced, iodide is preferentially bound.

## 2.5. Nucleophilicity Parameters and the *trans* Effect

To quantitatively compare the relative nucleophilic abilities of various ligands, a nucleophilicity scale<sup>[15]</sup> has been established based on Pt<sup>II</sup> centers.<sup>[16]</sup> In accord with the *soft* nature of the Pt<sup>II</sup> center, iodide possesses the largest nucleophilicity parameter. Other quantitative results have only been ob-

Table 3. Rates of aquation  $k_{aq}$  [ $10^7 s^{-1}$ ] of complexes  $[M(NH_3)_5X]^{2+}$  with displacement of  $X^-$  at 25 °C.

|    | Co <sup>III</sup> | Cr <sup>III</sup> | Ru <sup>III</sup> | Rh <sup>III</sup> | Ir <sup>III</sup> |
|----|-------------------|-------------------|-------------------|-------------------|-------------------|
| I  | 83                | 10000             | 2.5               | 0.062             | 0.0019            |
| Br | 39                | 950               | 9.8               | 0.34              | 0.011             |
| Cl | 18                | 95                | 7.1               | 0.48              | 0.011             |
| F  | 0.86              | 2.5               | –                 | –                 | –                 |

tained for Au<sup>III</sup> centers<sup>[17]</sup> (which parallel the relative values observed for Pt), and this trend can be expected to be similar for other square-planar complexes containing soft transition metals.

The *trans* effect<sup>[18]</sup> is another important property of ligands that shows a distinct trend within the halide group. The *trans* effect is defined as “the effect of a coordinated group on the rate of substitution reaction of ligands *trans* to itself.”<sup>[19]</sup> The relative *trans* effect of the halides has been determined quantitatively for Pt<sup>II</sup> centers, with iodide possessing the largest *trans* effect. This trend for the halide group is related to their  $\sigma$ -donating ability since ligands which are strongly  $\sigma$  donating will strengthen their bond to the metal at the expense of the ligands *trans* to them. Indeed, calculations of the overlap between the  $\sigma$ -donor orbital of the halide ligands and the Pt6p<sub>o</sub> orbitals showed that there was increasing overlap on going from Cl to I.<sup>[20]</sup>

### 3. Halide Ligands and Stoichiometric Processes

#### 3.1. Electron Donation and Ease of Metal Oxidation

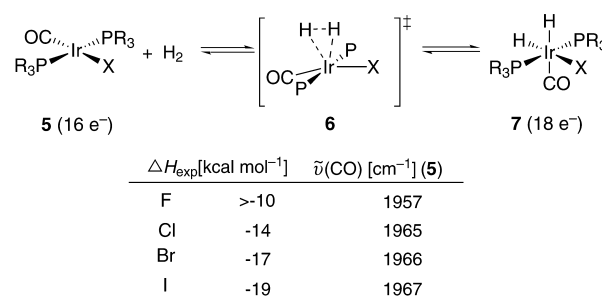
An increase in electron density at the metal center will facilitate oxidative processes.<sup>[21]</sup> When the effects of halide ligands on oxidative processes are considered, it is the ability to participate in  $\pi$  donation that predominates. For example, electrochemical studies on [Cp<sub>2</sub>MX<sub>2</sub>] (M = Nb, Ta; Cp = C<sub>5</sub>H<sub>5</sub>)<sup>[22]</sup> and [Cp<sub>2</sub>WX(R)]<sup>[23]</sup> revealed that the ease of oxidation increased I < Br < Cl. In another study,<sup>[24]</sup> it was found that reversible oxidation of [Cp\*Fe(dppe)X] (dppe = bis(diphenylphosphino)ethane; Cp\* = C<sub>5</sub>Me<sub>5</sub>) to the mono- and dicationic species occurs most readily for the most electronegative but best  $\pi$ -donating halide, F, and becomes more difficult down the series. It was also determined that as a result of the one- and two-electron oxidations, the Fe–X bonds were weakened with the Fe–F bond weakening the least—again indicating the pronounced effect of halide-to-metal  $\pi$  donation which becomes more significant with the removal of electrons.

#### 3.2. Hydrogen Addition/Elimination

The effects of the halide ligands on the reactivity of *trans*-[Ir(PR<sub>3</sub>)<sub>2</sub>(CO)X], [IrXH<sub>2</sub>(PR<sub>3</sub>)<sub>2</sub>], and *trans*-[M(PMe<sub>3</sub>)<sub>4</sub>X<sub>2</sub>] (M = Mo, W) towards hydrogen addition illustrate very well the concepts described in previous sections. To explain the observed trends, halide–metal  $\pi$  donation as well as push–pull and filled–filled interactions must be considered. Furthermore, they underline the point that by changing the halide ligand, dramatic effects on the reactivity can be obtained. They also demonstrate that these influences may not be the same for a given reaction when performed with different transition metal systems.

The dependence of the rate of oxidative addition of hydrogen to *trans*-[Ir(PR<sub>3</sub>)<sub>2</sub>(CO)X] (Vaska-type complexes) on the halide ligand has been studied in detail. Both experimental<sup>[25]</sup> and computational<sup>[26]</sup> studies reveal that the

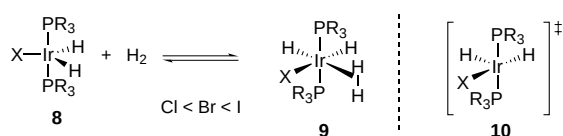
addition of H<sub>2</sub> is most exothermic when X = I.<sup>[27]</sup> While oxidative addition should be favored by ligands which increase the electron density at the metal,<sup>[28]</sup> the trend here appears to contradict this expectation since F, the strongest  $\pi$  donor, produces the least energetically favorable reaction. To verify that the relative  $\pi$ -donating abilities of the halides followed the anticipated trend, the  $\nu$ (CO) stretching frequencies were examined for **5**. These frequencies indicate that the electron density at the metal does indeed increase according to the predicted ability of the halides to donate electron density by  $\pi$  donation (I < Br < Cl < F) exactly *opposite* to the observed trend in reactivity (Scheme 7).<sup>[29, 30]</sup> This discrepancy is best explained by appreciating how changes in the coordination geometry affect the role of the  $\pi$  donation.



Scheme 7. Halide effects in hydrogen addition to Vaska's complex.

Goldman and Krogh-Jespersen have demonstrated that Ir–X  $\pi$  interactions dominate the thermodynamics of H<sub>2</sub> addition in at least three ways. First,  $\pi$  donation, made possible on the square-planar complex through the presence of the  $\pi$ -acid CO ligand, can stabilize the 16-electron d<sup>8</sup> square-planar complex **5**. Thus **5** will be most stable when X = F. Second,  $\pi$  donation will destabilize the 18-electron d<sup>6</sup> H<sub>2</sub>-addition product **7** through filled–filled interactions. Complex **7** will therefore be least stable when X = F. Third,  $\pi$  donation was also found to influence the energy of the transition state **6**. In the starting material **5**,  $\pi$  bonding occurs as a result of the push–pull interactions between the *trans* halide and carbonyl ligands. This effect is highly directional and will be maximal when the ligands are *trans* to each other. To reach the transition state, a bending of the X–Ir–CO unit is required. This bending will diminish the stabilizing push–pull interactions and will become more disfavored as  $\pi$  donation increases, reaching a maximum when X = F. An argument is also made that the reactivity would be reduced as a result of an increase in the HOMO–LUMO gap because of  $\pi$  donation.<sup>[31]</sup> Since fluoride is the best  $\pi$  donor, the combination of these  $\pi$  effects will make H<sub>2</sub> addition to the fluoro-complex the least favorable of the halide series.

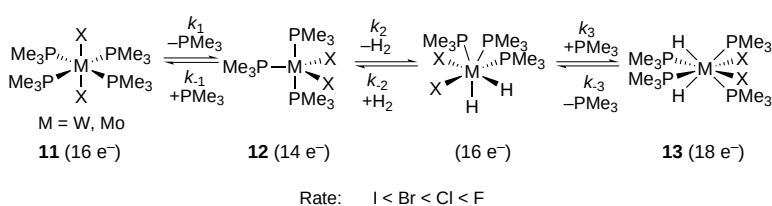
In a second example, the rate of H<sub>2</sub> addition to [IrXH<sub>2</sub>(PR<sub>3</sub>)<sub>2</sub>] (**8**) was found to vary with X, the rate being most favorable when X = I (Scheme 8).<sup>[32]</sup> This reaction has been studied computationally.<sup>[33]</sup> To accommodate H<sub>2</sub> binding, distortion of the Ir trigonal-bipyramidal complex **8** towards the T<sub>H</sub>-shaped (a square pyramid with an H atom at the apex) transition state **10** was proposed.<sup>[34]</sup> While halide to metal  $\pi$  donation can occur in **8**, this interaction is either



Scheme 8. Halide effects in hydrogen addition to  $[\text{IrXH}_2(\text{PR}_3)_2]$  and the  $\text{T}_\text{H}$  transition state **10**.

partially or completely disrupted in the T-shaped transition state.<sup>[35]</sup> It is therefore more energetically difficult to reach the transition state as the level of  $\pi$  donation increases, and will be most difficult for Cl and F ligands. Furthermore, the distortion to the T-shaped transition state places the hydride and the halide *trans* to one another. Since the hydride is a strong  $\sigma$  donor, placing iodide *trans* to it will be more favorable than chloride, because iodide is more polarizable and can therefore better adapt to the bonding requirement of the *trans* hydride. The stability of the product complex **9** will also be affected by the nature of the halide ligand. Since it is an 18-electron  $\text{d}^6$  six-coordinate complex, any  $\pi$  donation from the halide ligand will result in filled–filled destabilizing interactions. The strongest  $\pi$  donors, Cl and F, will most disfavor the formation of **9**.

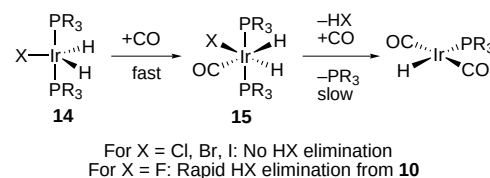
Friesner, Parkin, and co-workers have recently reported that the energetics of  $\text{H}_2$  addition to **11** depend strongly on the halide, the addition being most exothermic for  $\text{X} = \text{F}$  (Scheme 9).<sup>[36]</sup> This trend is opposite to that found for Vaska's complex where the fluoride complex produces the least favorable reaction. To explain this difference, both the steric and the electronic properties of the halide ligands must be considered. Since fluoride is the smallest of the halides its presence would minimize the steric interactions on the highly congested eight-coordinate product complex **13**. From an electronic point of view, fluoride ligands will destabilize the starting material complex **11** through filled–filled interactions and make it more reactive towards phosphane dissociation. This destabilization would be less pronounced with the heavier halides. Fluoride would also best stabilize the unstable 14-electron intermediate **12** by  $\pi$  donation.



Scheme 9. Halide effects in hydrogen addition to  $\text{trans}-[\text{M}(\text{PMe}_3)_4\text{X}_2]$  ( $\text{M} = \text{Mo}, \text{W}$ ).

### 3.3. HX Elimination

Caulton has studied the effect of halide ligands on the rate of HX elimination from  $[\text{Ir}(\text{H})_2\text{X}(\text{PtBu}_2\text{Ph})_2]$  (**14**) which is promoted by CO coordination (Scheme 10).<sup>[37]</sup> Experimental results confirmed the prediction that upon coordination of the CO ligand, the destabilization created by filled–filled interactions involving the orbitals of the X ligand at the 18-electron  $\text{d}^6$  six-coordinate metal center affect the rate of HX

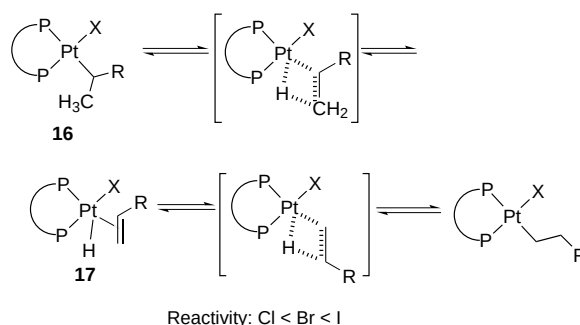


Scheme 10. Halide effects in HX elimination.

elimination. With the weaker  $\pi$  donors (Cl, Br, I), no HX elimination was observed from **15**. With fluoride, on the other hand, rapid HX elimination was observed after a few minutes at room temperature, which correlates well with the strong  $\pi$ -donating ability of fluoride relative to the heavier halides.

### 3.4. $\beta$ Hydride Elimination

Recent studies of  $\beta$  hydride migrations in  $[\text{PtL}_2(\text{X})\text{CHRCH}_3]$  (**16**) have revealed a dependence of rate on the nature of the halide (Scheme 11).<sup>[38]</sup> The mechanism of these transformations shows that the intermediate five-coordinate complex **17** (of undefined geometry) is present



Scheme 11. Halide effect on the rate of  $\beta$ -hydride elimination.

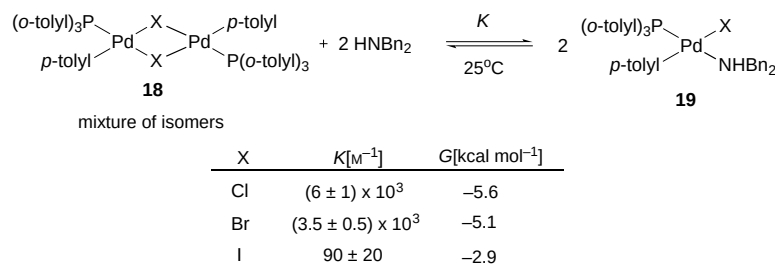
in both forward and reverse processes. The rate dependence was proposed to be a function of the stability of this complex. It was shown for other five-coordinate palladium complexes that their stability increases in the order  $\text{Cl} < \text{Br} < \text{I}$ .<sup>[39]</sup> Thus, if the stability of intermediate **17** is affected analogously, the rate would be influenced correspondingly, being fastest for  $\text{X} = \text{I}$ .

### 3.5. Formation and Cleavage of Metal–Halide Dimers

In many catalytic processes, dimeric catalyst precursors are used or such species are implicated along the reaction pathway. While dimeric complexes are rarely the active species, their relative stability can influence the rate of the transformation by acting as a reservoir or resting position during the catalytic cycle. Experimental evidence has shown that the stability of these dimers changes dramatically with the nature of the halide, being most stable when bridged by iodide ligands.

While studying aryl amination reactions, Buchwald found that the nature of the halide affects the cleavage of the complexes **18**.<sup>[40]</sup> When dimeric palladium complexes **18** were treated with dibenzylamine, monomer formation was found to be most favorable for X = Cl (Scheme 12). It was also found that reaction with smaller amines, such as dibenzylamine, favored cleavage more than larger ones, such as diisopropylamine. Furthermore, this difference in reactivity was more enhanced when X = I than when X = Cl.

Buchwald explained these trends based on the relative polarizability and size of the halides. The dative Pd-( $\mu$ -X) bond strengths should parallel the donor ability of the halide lone-pair electrons and therefore be strongest when X = I.



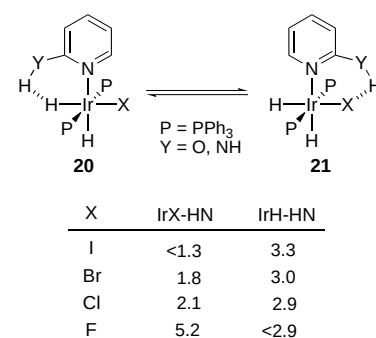
Scheme 12. Effect of halide on the cleavage of dimers.

The dependence of the rate of dimer cleavage on the size of the amine and the halide ligand can be explained as follows: since the amine and the halide ligands are *cis* in the monomeric species **19**, a larger halide will create a weaker Pd–N bond and disfavor cleavage. Furthermore, large amines should promote Pd–N bond weakening since steric interactions with the halide would be more severe.

The stability of iodide-bridged dimers has been documented elsewhere.<sup>[41,42]</sup> For example, when PdI<sub>2</sub> is treated with excess P(*o*-tolyl)<sub>3</sub>, only the dimeric species is obtained. On the other hand, when PdBr<sub>2</sub> or PdCl<sub>2</sub> are used, only the monomers, [Pd{P(*o*-tolyl)<sub>3</sub>}<sub>2</sub>X<sub>2</sub>], are formed.<sup>[41]</sup> Chatt and co-workers also observed that treatment of dimeric [(PnPr<sub>3</sub>)<sub>2</sub>Cl]<sub>2</sub> with *p*-toluidine formed the stable amine monomer [Pd(PnPr<sub>3</sub>)<sub>2</sub>(*p*-toluidine)Cl] while reaction of the iodide-bridged dimer produces an equilibrium mixture of starting material and the monomeric species [Pd(PnPr<sub>3</sub>)<sub>2</sub>(*p*-toluidine)I].<sup>[42]</sup>

### 3.6. Hydrogen Bonding and Protonation

Hydrogen bonding has been shown to occur between weak acids, such as OH and NH, and transition metal complexes, either at the metal center itself or at its ligands.<sup>[43]</sup> A quantitative study, by Eisenstein and Crabtree, designed to examine competitive hydrogen bonding to halide and hydride ligands is illustrative.<sup>[44]</sup> By determining the relative population of the two isomers **20** and **21**, the relative ability of the halide ligand to participate in hydrogen bonding could be deduced. A distinct trend was found within the halide series, with fluoride being most able to participate in H bonding (Scheme 13). Additional experimental evidence for consider-



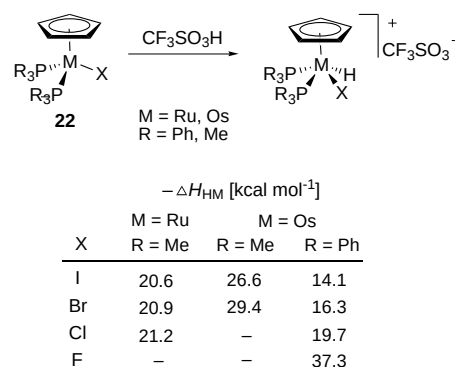
Scheme 13. Relative ability of the halides to H bond. The Table shows the calculated bond strengths of the H bonds [ $kcal\ mol^{-1}$ ].

ing these halide hydrogen-bonding interactions is revealed by the increasing number of crystal structures of transition metal complexes which contain these bonds.<sup>[45]</sup>

Eisenstein and Crabtree also found that the halide ligand on **20** and **21** influenced the ability of the hydride ligand *trans* to the halide to hydrogen bond, with the iodo complex producing the strongest iridium–hydride–H bonds. This result was rationalized in terms of the relative *trans* influence of the halides. A larger *trans* influence would

lengthen the *trans* Ir–H bond and displace electron density towards the hydride ligand. This increase in electron density would result in an increase in the ability of the hydride ligand to hydrogen bond. Iodide, which possesses the largest *trans* influence of the halides, is thus the most able to increase the H-bond strength at the *trans* hydride ligand.

Angelici has reported the enthalpies of protonation for a wide variety of transition metal complexes, and these too were found to be influenced by the halide ligand.<sup>[46]</sup> For ruthenium and osmium complexes of type **22**, the basicity was found to be highest when X = F (Scheme 14) and this was rationalized



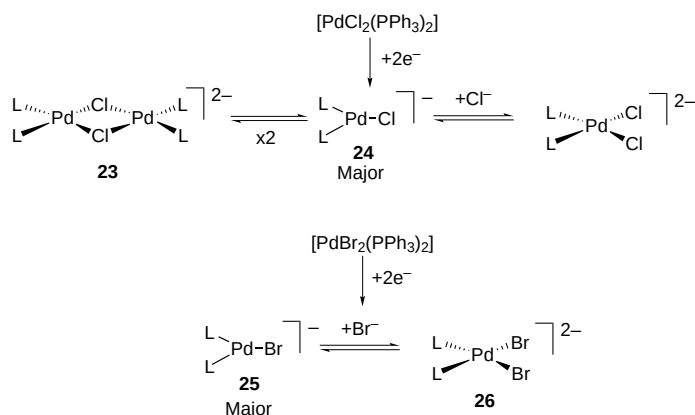
Scheme 14. Influence of halide ligand on the enthalpy of protonation.

in terms of electronic and steric effects. From an electronic point of view, fluoride is the strongest  $\pi$  donor and should therefore most increase the electron density at the metal center. From a steric point of view, fluoride would result in the least steric congestion as the complex coordination number increases and less space is available within the coordination sphere.

### 3.7. Generation of Anionic Palladium(0) and Oxidative Insertion

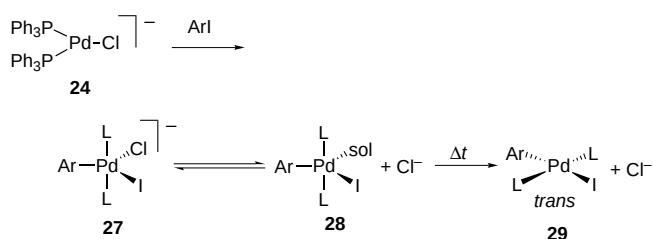
Palladium(0) is ubiquitous in transition metal catalysis. A number of methods are used to access this species, these include the use of  $[\text{Pd}(\text{PPh}_3)_4]$  and  $[\text{Pd}_2(\text{dba})_3]$  (dba = dibenzylacetone), or reduction of  $[\text{Pd}(\text{OAc})_2]$  and  $[\text{PdL}_2\text{Cl}_2]$  complexes. It has been demonstrated that when  $[\text{Pd}(\text{PPh}_3)_4]$  is used (under certain conditions), the coordinatively unsaturated 14-electron  $[\text{Pd}(\text{PPh}_3)_2]$  species is the active catalyst, even though it is present in very small amounts as a result of the unfavorable endergonic processes required for its generation.<sup>[47]</sup> Amatore and Jutand have recently shown that when in situ reduction of the  $\text{Pd}^{\text{II}}$  complexes is used to generate  $\text{Pd}^0$ , anionic species are generated instead of the neutral  $[\text{Pd}(\text{PPh}_3)_2]$  complex.<sup>[49]</sup> Furthermore, the nature of the halide was found to influence the reactivity of these palladate intermediates.

When the complexes  $[\text{PdX}_2(\text{PPh}_3)_2]$  ( $\text{X} = \text{Cl}, \text{Br}$ )<sup>[48]</sup> are reduced electrochemically, mixtures of anionic complexes are formed, the nature of which depends on the halide found on the precursor.<sup>[49]</sup> The effect of halide binding was found to have a stabilizing effect on the  $[\text{Pd}(\text{PPh}_3)_2]$  moiety since the reduced species did undergo rapid reaction to form metallic palladium. For example, when  $[\text{PdCl}_2(\text{PPh}_3)_2]$  is reduced, an equilibrium mixture of two monomeric and one dimeric species is formed where the predominant species is  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}]^-$  (**24**). With  $[\text{PdBr}_2(\text{PPh}_3)_2]$ , only the monomeric species **25** and **26** are produced (Scheme 15).<sup>[49d]</sup>



Scheme 15. Anionic palladium(0) species generated through reduction of  $[\text{PdX}_2\text{L}_2]$  species.

The reactivity of these equilibrium mixtures was investigated with respect to oxidative addition to phenyl iodide.<sup>[49c]</sup> Commencing with anionic  $\text{Pd}^0$  complex **24** prepared in situ, oxidative addition of  $\text{PhI}$  generates a five-coordinate 18-electron anionic complex **27** where both the chloride and the iodide ligands remain bound (Scheme 16). Intermediate **27** is then involved in an equilibrium that generates neutral species **28** where the chloride ion has dissociated and is replaced by a solvent molecule. Subsequently, the *trans* square-planar complex **29** is produced. It was found that the addition of

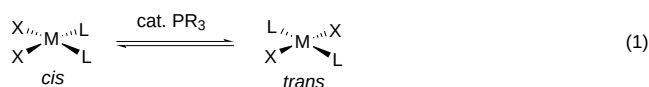


Scheme 16. Oxidative addition of  $\text{PhI}$  to  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}]^-$ .  $\Delta t$  tends to be in the region of several hours.

chloride ions inhibits the generation of **29**. Of the three chloride species generated by the reduction of  $[\text{PdCl}_2(\text{PPh}_3)_2]$ , the dimer **23** is the most reactive, but because of its low concentration under typical conditions, its contribution is small compared to the major species **24**. Furthermore,  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}]^-$  was found to be more reactive than  $[\text{Pd}(\text{PPh}_3)_2\text{Br}]^-$  towards oxidative addition with  $\text{PhI}$ . These results will be discussed further in Section 4.2.4.

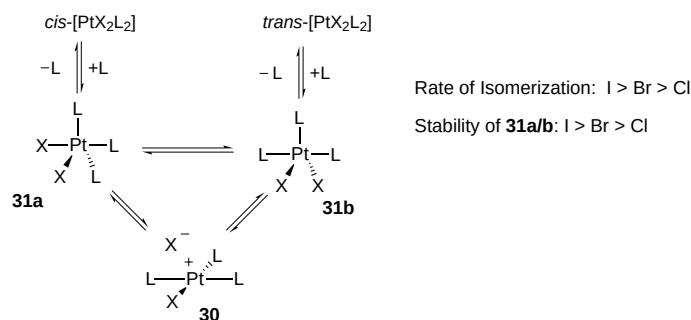
### 3.8. *cis*–*trans* Isomerization at Square-Planar $d^8$ Complexes

The mechanism of phosphane catalyzed *cis*–*trans* isomerizations of square-planar  $d^8$  complexes has been the focus of detailed study [Eq. (1)  $\text{X} = \text{halide}$ ,  $\text{L} = \text{phosphane}$ ,  $\text{M} = \text{Pd}^{\text{II}}$ ,  $\text{Pt}^{\text{II}}$ ]. Instead of one distinct mechanism emerging, conflicting



results and interpretations have led to the proposal of at least four different possibilities<sup>[50]</sup> with each likely occurring to some extent depending on the exact conditions used during the study.<sup>[51]</sup> A feature of the associative mechanism is the transiency or intermediacy of a five-coordinate species  $[\text{ML}_3\text{X}_2]$ . The nature of the  $\text{X}$  ligand was found to influence the rate and probably the mechanism of these isomerizations.

Most mechanistic discussion has focused on the consecutive-displacement<sup>[50a–c]</sup> and pseudorotation<sup>[50f–i]</sup> pathways (Scheme 17) and it has been proposed that the dominant



Scheme 17. Mechanism of phosphane/halide-catalyzed *cis*–*trans* isomerization of  $[\text{PtX}_2\text{L}_2]$ .

pathway depends on the coordinating ability of the X ligand, the basicity of the L ligand, and the polarity of the solvent.<sup>[50]</sup> For example, it has been determined that the rate of isomerization is fastest when X=I. This result has been explained<sup>[50i, 52]</sup> as being a function of two factors. First, the five-coordinate complex is most stabilized when X=I, thus allowing sufficient time for pseudorotation to occur. Second, I<sup>−</sup> is the most nucleophilic of the halides. Following the consecutive-displacement mechanism, this would mean that displacement of a more strongly bound neutral ligand on **30** will be fastest when X=I.

The intermediacy of complexes **30** and **31a/b** warrants consideration since analogous five-coordinate complexes can be invoked as intermediates in other palladium-catalyzed transformations. Regardless of the exact mechanism, experimental evidence has revealed a significant halide effect in determining the complex that will most likely be formed. X-ray crystal structures have been determined for several compounds of empirical formula [MX<sub>2</sub>L<sub>3</sub>] **31a/b** when X=Cl and Br.<sup>[50i, 52, 53]</sup> In each case, the complexes exhibited a distorted square-pyramidal structure with the halide being located at the apex. Importantly, the metal–halide bond length at the apex was longer than the sum of the ionic radii calling into question whether these complexes are really five-coordinate or actually ionic and better described as [MXL<sub>3</sub>]<sup>+</sup>X<sup>−</sup>. It has been pointed out, however, that while ion pairs are traditionally described as outer-sphere complexes, ion-pairs of four-coordinate complexes would probably not meet this description because of the coordinative unsaturation of d<sup>8</sup> complexes which allows the counter ion to enter the coordination sphere.

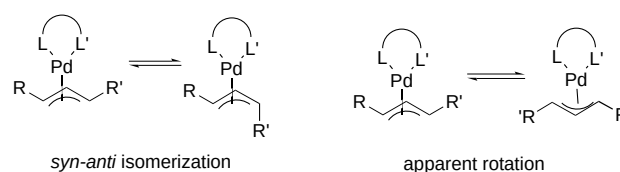
Roulet et al. have reported mechanistic studies of the phosphane-catalyzed *cis*–*trans* isomerization of square-planar [PtX<sub>2</sub>L<sub>2</sub>] complexes (X=Cl, Br, I; L=PMe<sub>3</sub>, PEt<sub>3</sub>, P(*n*Bu)<sub>3</sub>, P(*o*-tol)<sub>3</sub>).<sup>[52]</sup> When X=Cl or Br, the only species detectable in solution that contains three phosphanes was the square-planar **30**. However, when X=I, [PtI<sub>2</sub>(PMe<sub>3</sub>)<sub>3</sub>] could be detected as a five-coordinate complex in solution. Furthermore the addition of increasing amounts of NBu<sub>4</sub>I to a solution of [PtI(PMe<sub>3</sub>)<sub>3</sub>]PF<sub>6</sub> gradually shifts the <sup>31</sup>P{<sup>1</sup>H} NMR spectrum to that corresponding to the five-coordinate species [PtI<sub>2</sub>(PMe<sub>3</sub>)<sub>3</sub>]. Although phosphane displacement is not observed at −60 °C, NMR spectroscopic analysis determined that fast exchange of I<sup>−</sup> ions was occurring between the four- and five-coordinate complexes.

Studies have revealed that both steric<sup>[54]</sup> and electronic<sup>[55]</sup> factors play a role in determining whether a d<sup>8</sup> complex will be four- or five-coordinate. Larger ligands will favor the four-coordinate form so as to minimize steric interactions. From an electronic point of view, strong σ-donor and π-acidic ligands are expected to favor five-coordinate complexes. In the case of the halides, it appears that the electronic factors dominate since iodide results in the most stable five-coordinate complexes and iodide is the strongest σ donor. The halides are π donating, so they would all be expected to disfavor five-coordinate complexes, but since iodide is the weakest π donor this destabilization would be smallest when X=I. It is important to note that the size of the neutral ligands will also influence the relative stability of the four- and five-coordinate

complexes. As these ligands become larger, the four-coordinate form will become increasingly preferred and the five-coordinate form increasingly short-lived.

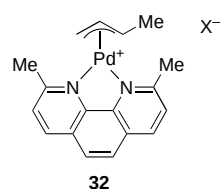
### 3.9. Isomerizations of π-Allyl Palladium Complexes

Significant advances towards an understanding of the mechanism of π-allyl palladium transformations have been made through the use of solution NMR spectroscopy and X-ray crystallographic analysis. The ability to isolate crystalline π-allyl intermediates was facilitated by the use of noncoordinating counter ions. As a result of the mechanistic work on π-allyl palladium species two key dynamic processes were revealed: *syn*–*anti* isomerization and apparent rotation (or *syn*,*syn*–*anti*,*anti* exchange; Scheme 18).<sup>[56]</sup>



Scheme 18. Important dynamic processes of π-allyl complexes.

In the studies of these two processes, a dramatic influence of the counter ion on the rate was observed.<sup>[57]</sup> For example, the *syn*–*anti* isomerization of complex **32** (BF<sub>4</sub><sup>−</sup> counter ion) was found to be slow at room temperature facilitating isolation of the pure *syn* and *anti* isomers (Scheme 19).<sup>[58]</sup> At 60 °C slow isomerization was observed to afford an equilibrium mixture (2:1 ratio) of *syn*:*anti* **32** after several hours.

| <br><b>32</b> | Counter Ion (X <sup>−</sup> ) | Properties                                                       |
|---------------------------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------|
|                                                                                                   | BF <sub>4</sub> <sup>−</sup>  | Inert toward isomerization at 298K<br>Slow isomerization at 333K |
|                                                                                                   | Cl <sup>−</sup> (4 mol%)      | Complete isomerization within minutes at 298K                    |

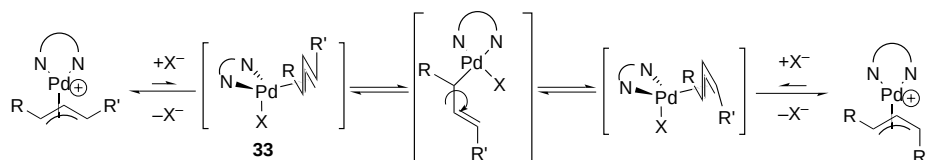
Scheme 19. Effect of chloride on *syn*–*anti* isomerization.

Importantly, when only 4 mol% Cl<sup>−</sup> ion was added to the BF<sub>4</sub><sup>−</sup> salt, complete equilibration was observed within minutes at room temperature. It was also determined that changing the solvent from tetrachloroethane to D<sub>2</sub>O decreased the rate of isomerization by two orders of magnitude. This effect was attributed to the ability of water to stabilize the cationic four-coordinate π-allyl complex by efficiently solvating the ions and preventing the chloride from entering the palladium coordination sphere.<sup>[57c]</sup>

Insight into the mechanistic pathway was gained when it was determined that the entropy of activation for *syn*–*anti* proton exchange is negative; indicative of an associative process, opposite to that expected for the η<sup>3</sup>–η<sup>1</sup>–η<sup>3</sup> rearrangement<sup>[59]</sup> which results in an increase in entropy on conversion into the η<sup>1</sup>-form. Furthermore, the rate of isomerization was

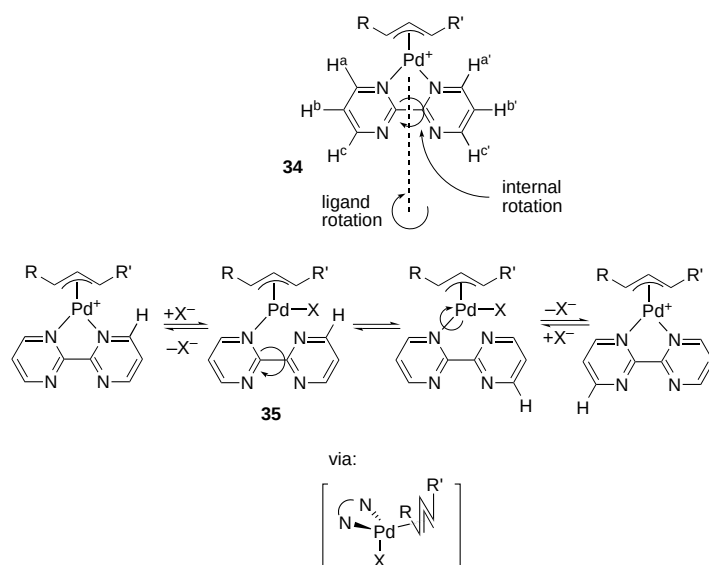
found to increase proportionally to the amount of chloride added. These findings support the intermediacy of five-coordinate species **33** (Scheme 20). Intermediate **33** could then adopt the  $\eta^1$ -form reestablishing the four-coordinate square planar geometry and undergo subsequent *syn*–*anti* isomerization.

The mechanism established for the apparent rotation of  $\pi$ -allyl palladium species is analogous to that described above for the *syn*–*anti* isomerization.<sup>[60]</sup> Conclusive evidence for dissociation of one of the nitrogen atoms of the neutral ligand was obtained by solution NMR spectroscopy analysis for



Scheme 20. Mechanism of *syn*–*anti* isomerization.

complex **34** (Scheme 21).<sup>[57d]</sup> At room temperature, only two aromatic protons were observed in a 2:1 ratio indicating that protons H<sup>a</sup>, H<sup>a'</sup>, H<sup>c</sup>, and H<sup>c'</sup> were chemically equivalent. For H<sup>a</sup> to be equivalent to H<sup>a'</sup> (and similarly H<sup>c</sup> to H<sup>c'</sup>)



Scheme 21. Mechanism of apparent rotation.

dissociation of one nitrogen atom must occur. The dissociated neutral four-coordinate species **35** is then free to undergo both internal and ligand rotation to make the protons equivalent in accord with the NMR spectroscopy observations. As with *syn*–*anti* isomerization, the rate of this exchange was found to be slow when the counter ion was noncoordinating and fast when chloride ions were added. The intermediacy of a five-coordinate species again explains these results. The same observations and explanations were made with respect to methyl exchange when tetramethylethylenediamine (TMEDA) is used as the ligand.

## 4. Catalytic Processes: Improving Reactivity Through the Application of Halide Effects

### 4.1. Halide Ligands and Asymmetric Catalysis

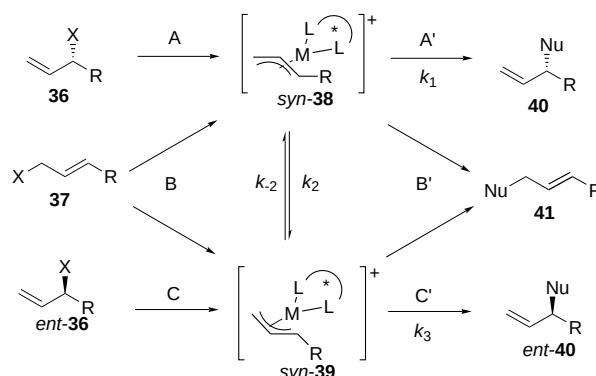
#### 4.1.1. Palladium-Catalysis

##### 4.1.1.1. Asymmetric Allylic Alkylations

Allylic bond formation through the intermediacy of  $\pi$ -allyl palladium complexes is an important synthetic transformation and remains an area of intense research.<sup>[61]</sup> Catalytic reactions, particularly enantioselective variants, based on the pioneering work of Tsuji and Trost<sup>[62]</sup> have received the most focus. While it is possible to pinpoint the source of enantioselectivity in several transition metal catalyzed processes, it is a much more complicated issue with allylic alkylations. In these processes,

one or several of the steps in the mechanism may be the enantiodiscriminating step(s).<sup>[63]</sup> The choice of metal can also influence the nature of the enantioselective step through a change in reaction mechanism.<sup>[64, 65]</sup>

The issue is further complicated when substrates generate nonsymmetrical  $\pi$ -allyl intermediates since the complexes no longer possess a plane of symmetry when  $C_2$ -symmetric ligands are used. These substrates also give rise to regioselectivity issues since the two terminal carbons of the  $\pi$ -allyl group are not equivalent. These complexities are illustrated in Scheme 22. Upon reaction of the chiral  $\pi$ -allyl precursors, **36** and *ent*-**36**, displacement of the leaving group and inversion would generate predominantly *syn*-**38** and *syn*-**39** by pathways A and C respectively. The  $\pi$ -allyl precursor **37** is not chiral so displacement can occur from either olefinic face generating both *syn*-**38** and *syn*-**39**. At this point, nucleophilic attack with inversion could occur at the more substituted terminus of the  $\pi$ -allyl moieties to give **40** and *ent*-**40** (paths A' and C'). If nucleophilic attack occurs at the less substituted terminus, achiral **41** would be generated from both intermediates (path B').

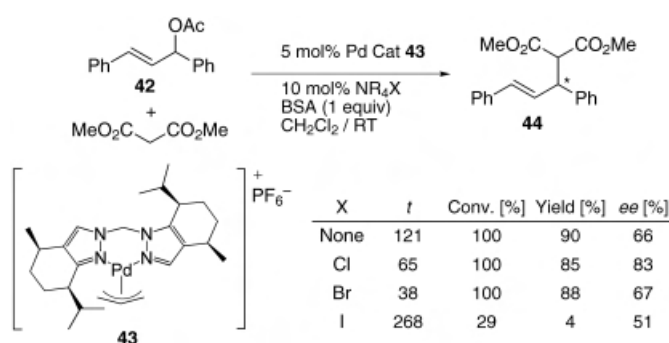


Scheme 22. Factors affecting regio- and enantioselectivity of allylic substitution reactions. Nu = nucleophile.



Regioselectivity issues aside, two key prerequisites must be established for high enantioselectivity to be obtained in the formation of **40** commencing from *rac*-**36**. First, the chiral ligand must impart a sufficiently large difference in the rates of nucleophilic attack such that  $k_1 \gg k_3$  or  $k_3 \gg k_1$ . Second, the rate of isomerization between the  $\pi$ -allyl intermediates,  $k_2$  and  $k_{-2}$ , must be fast compared to nucleophilic attack, that is, Curtin–Hammett conditions must be established.<sup>[66, 67]</sup> The processes for the interconversion of *syn*-**38** and *syn*-**39** and the role that halides can play in them are discussed in Section 3.9.

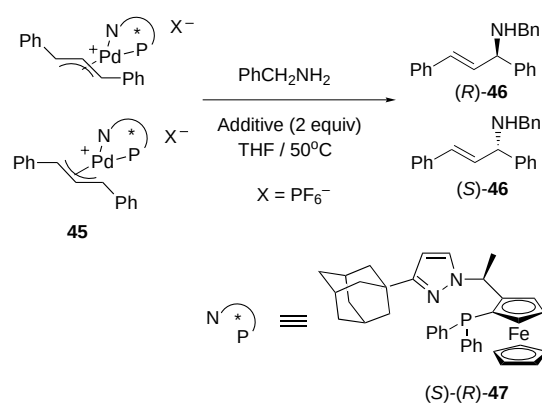
The first example of halide effects in asymmetric allylic alkylation reactions was reported in 1993.<sup>[68]</sup> In the reaction of **42** with dimethylmalonate in the presence of catalytic **43**, Togni and co-workers found that both the rate and the enantioselectivity were effected by the presence of added halides (Scheme 23). In the absence of added halide, complete



conversion was observed after 121 hours and the desired product **44** was obtained in 90% yield and 66% *ee*. Better results were obtained when 5 mol% tetraethylammonium chloride was added. In this case, the reaction time shortened to 65 hours and the *ee* value increased to 83%. Bromide induces slightly lower levels of enantioselectivity but a faster reaction, and iodide was found to be the worst, acting to poison the catalyst and lower the enantioselectivity to a lower level than when no halide additive was used.

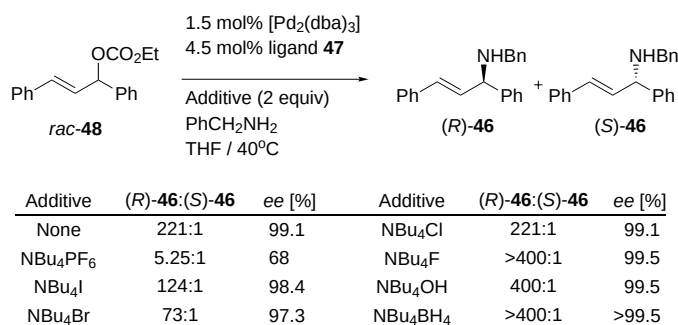
Another example of these halide effects was found by Togni and co-workers while working to understand the sense of induction in allylic alkylations of complex **45**.<sup>[69]</sup> When **45** is generated catalytically in situ, high enantioselectivities are observed for the generation of (*R*)-**46**. When the PF<sub>6</sub><sup>−</sup> salt of **45**, isolated as a mixture of predominantly two isomers, is subjected to the reaction conditions, (*R*)-**46** is produced in <10% *ee*. To explain these results, two types of experiment were preformed to determine the influence of anions on the reaction outcome. In the first approach, the nucleophile was added to complex **45** (two isomers) along with various additives (Scheme 24). In the absence of any additive, **45** reacted to give (*R*)-**46** in 6.7% *ee*. When two equivalents of fluoride were added, (*R*)-**46** was produced in 98.7% *ee*. With borohydride as a counter ion, the *ee* value reached >99.5%.

The second approach focused on the effects of salt additives on the catalytic reaction (which already showed a high



Scheme 24. Effect of halides on enantioselectivity (stoichiometric amount of palladium).

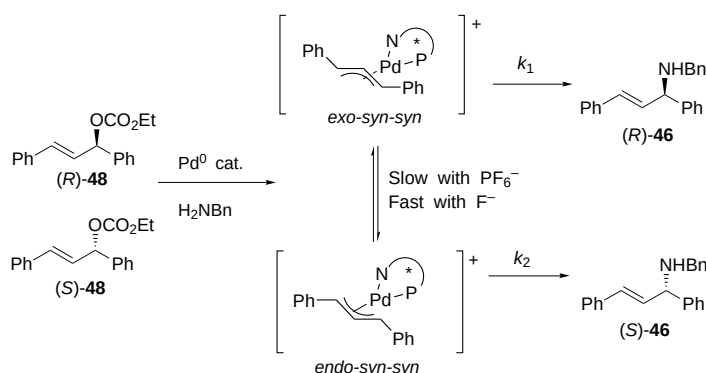
*ee* value). Again, the addition of small, hard anions caused an increase in the enantioselectivity (Scheme 25). It is intriguing that the addition of weakly coordinating counter ions caused a decrease in the enantioselectivity compared to when no additive was used.<sup>[70]</sup>



Scheme 25. Effect of halides on enantioselectivity (catalytic amount of palladium).

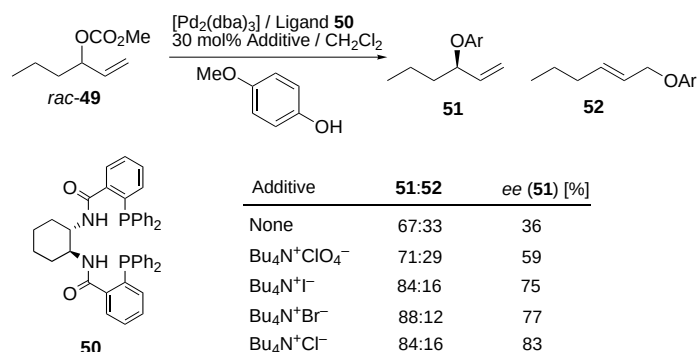
Togni argued that in the absence of coordinating counter ions, equilibration between the *endo-syn-syn* and the more stable *exo-syn-syn*  $\pi$ -allyl palladium intermediates is slow. Upon addition of such ions, however, interconversion becomes rapid compared to the rate of nucleophilic attack allowing Curtin–Hammett conditions to be established (Scheme 26).<sup>[71]</sup> These experiments clearly demonstrate the importance of fast equilibration of the  $\pi$ -allyl intermediates relative to nucleophilic attack for obtaining high enantioselectivity. Furthermore, they confirmed earlier predictions that the rates of apparent rotation and *syn*–*anti* isomerization are key factors to be considered in the development of new enantioselective  $\pi$ -allyl transformations.

Recent application of this concept to the more challenging unsymmetrically substituted substrates has been reported by Trost and Toste.<sup>[72]</sup> Here too, the addition of a catalytic amount of halide was found to beneficially influence both the



Scheme 26. Proposed role of the halide effect in the asymmetric allylic substitution.

regioselectivity and the enantioselectivity (Scheme 27). For example, when *rac*-**49** is treated with *p*-methoxyphenol in the presence of catalytic amounts of Pd<sup>0</sup> and chiral ligand **50** in dichloromethane, the two regioisomeric products **51** and **52** are produced in a 67:33 ratio with **51** formed in only 36% *ee*. Various salt additives were examined and it was found that chloride gave **51** and **52** in an 84:16 regioisomeric ratio with the major isomer produced in 83% *ee*. These results parallel those of Togni with the enantioselectivity being highest for X = Cl. The effect of fluoride was not reported.

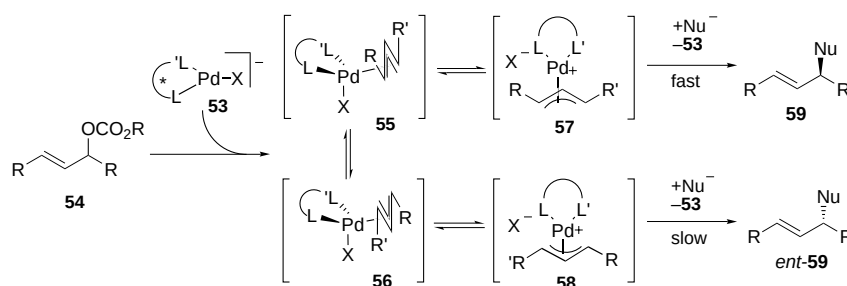


Scheme 27. Effect of halides on regio- and enantioselectivity.

Other factors that influence the selectivity of these transformations include the counter ion associated with the halide additives, the reaction concentration as well as the choice of solvent. All of these factors were found to influence the creation of Curtin–Hammett conditions.

Why it is that the lighter halides produce the highest enantioselectivities in  $\pi$ -allyl chemistry is a matter of conjecture. When the recent mechanistic work by Amatore and Jutand<sup>[49]</sup> on anionic palladium intermediates is taken into consideration along with the work done in studying the mechanism of *cis*–*trans* isomerization of d<sup>8</sup> square-planar complexes (Section 3.8), a slightly modified mechanistic pathway for the halide effect in  $\pi$ -allyl palladium chemistry

may be put forward (Scheme 28). The active catalyst could be an anionic palladium–halide complex **53**, analogous to the active species proposed for the palladium-catalyzed coupling reactions. The additional electron density resulting from the binding of the halide to the Pd<sup>0</sup> species should also make oxidative addition a more favorable process. The first species generated upon oxidative addition would thus be the neutral  $\pi$ -allyl complexes **55** and **56**. Loss of halide from **55** and **56** would produce **57** and **58** which would probably exist as ion pairs with the halide counter ion. Analogous to the *cis*–*trans* isomerization proposals, the coordinative unsaturation of the d<sup>8</sup> square-planar palladium complex may allow the halide to enter the coordination sphere facilitating the formation of the five-coordinate intermediates. Nucleophilic attack would most likely occur at the cationic complexes **57** and **58** since



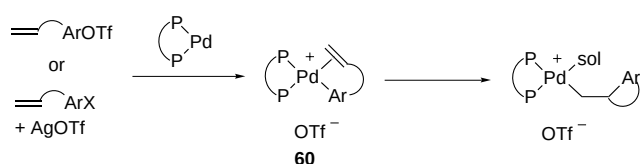
Scheme 28. Alternate mechanism for the halide effect in Pd-Catalyzed asymmetric allylic substitution.

they are more electrophilic. The anionic **53** would thus be regenerated and react with another **54**. Given that the environment around the metal center in **57** and **58** is likely to be sterically congested, the faster isomerizations by F and Cl may be in part because of their smaller size and better ability to form tight ion pairs. The ability of the halide to enter the coordination sphere would also influence the electrophilicity of complexes **57** and **58** by reducing the positive charge at the metal center. A less reactive  $\pi$ -allyl complex would enhance the ability of the system to attain Curtin–Hammett conditions.

#### 4.1.1.2. Asymmetric Heck Reactions

The Heck reaction has become an increasingly useful method of carbon–carbon bond formation and remains an exciting area of study in organic synthesis.<sup>[73, 74]</sup> Because these reactions were rarely used to generate stereocenters<sup>[75]</sup> and the belief that chelating bisphosphane ligands were unsuitable,<sup>[76]</sup> the first asymmetric Heck reactions were only described in 1989.<sup>[77]</sup> Since then, significant advances have been made and enantioselectivities in excess of 90% have been reported in certain cases.<sup>[78]</sup>

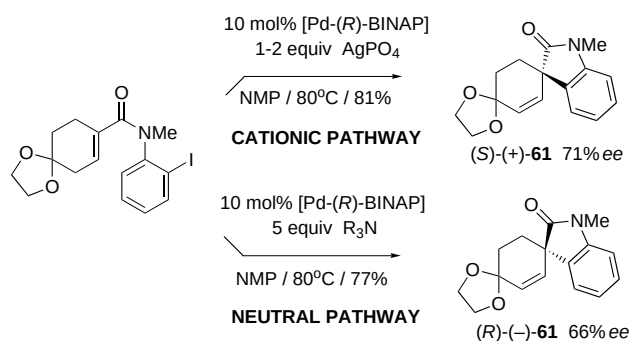
Some of the best results have been obtained using conditions where the reaction is believed to proceed by a cationic pathway (Scheme 29).<sup>[79]</sup> The use of aryl or vinyl triflates, or aryl or vinyl halides in combination with a halide scavenger (such as silver or thallium salts) frees a coordination site and facilitates binding of the chiral bidentate ligand,



Scheme 29. Cationic pathway for the asymmetric Heck reaction. OTf =  $\text{OSO}_2\text{CF}_3$  = triflate, sol = solvent.

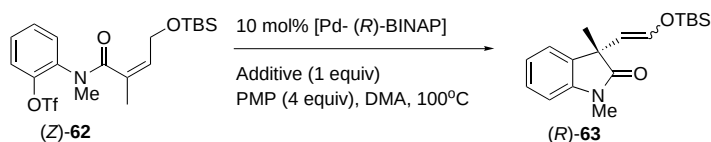
the olefin, and the aryl group to give the key  $\text{Pd}^{\text{II}}$  intermediate **60**.<sup>[80]</sup>

In 1992, Overman and co-workers reported an asymmetric Heck reaction that generated spiro-cycle **61**. In this case, it was found that either enantiomer could be formed with good selectivity using the same enantiomer of 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP) depending on the base used to scavenge HI (Scheme 30).<sup>[81]</sup> When silver salts were used, the reaction proceeded by the cationic pathway to produce (*S*)-(+)-**61** in 71% *ee*. When tertiary amines were used as the HI scavenger, (*R*)-(–)-**61** was generated in 66% *ee*. The iodide remains in the reaction mixture as an amine hydroiodide and could still interact with the palladium catalyst. Under these conditions, the reaction was suggested to proceed by a neutral pathway.



Scheme 30. Dependence of enantioselectivity on presence of halide ions. NMP = *N*-methylpyrrolidone.

Studies on a similar system also demonstrate the beneficial effects of added halides (Scheme 31). When aryl triflate **62** is subjected to palladium catalysis in the absence of any salt additives, the oxindole **63** is formed in 72% yield and 43% *ee*.

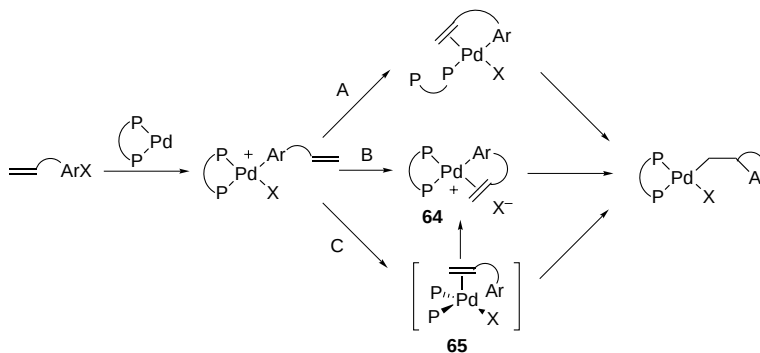


| Additive                 | Yield [%] | ee [%] |
|--------------------------|-----------|--------|
| None                     | 72        | 43     |
| $\text{Bu}_4\text{NOTf}$ | 70        | 42     |
| $\text{Bu}_4\text{NCl}$  | 52        | 93     |
| $\text{Bu}_4\text{NBr}$  | 59        | 93     |
| $\text{Bu}_4\text{NI}$   | 62        | 90     |

Scheme 31. Effect of added halides in the asymmetric Heck reaction. PMP = 1,2,2,6,6-pentamethylpiperidine, DMA = dimethylacetamide, TBS = *tert*-butyldimethylsilyl.

Addition of  $\text{Bu}_4\text{NOTf}$  (OTf =  $\text{OSO}_2\text{CF}_3$  = triflate) shows no improvement, but use of ammonium halides causes the enantioselectivity to increase to >90% *ee*.

Within the neutral pathway, there are at least three possible routes that could lead to product formation (Scheme 32). While path A had been the presumed mode of action for the neutral Heck reaction, this was ruled out as phosphane dissociation or partial dissociation would presumably result in



Scheme 32. Proposed reaction pathway under neutral conditions.

an erosion of enantioselectivity (verified experimentally by using mono-phosphane analogues of BINAP which gave lower levels of induction).<sup>[81d]</sup> Path B would lead to ionic intermediate **64** where the halide has dissociated from the metal center. This too was ruled out as similar selectivity should be expected from iodide salt **64** ( $\text{X} = \text{I}$ ) and triflate salt **60** if the counter ions were fully dissociated (supported experimentally). The authors favor Path C which passes through the pentacoordinate  $\text{Pd}^{\text{II}}$  species **65**. Since substitution chemistry at square-planar  $\text{Pd}^{\text{II}}$  species occurs predominantly through associative processes,<sup>[82]</sup> axial coordination of the olefin could occur giving rise to **65**. Migratory insertion at five-coordinate **65** is energetically less favorable,<sup>[83]</sup> thus direct product formation from **65** was ruled out. Another possibility is that displacement of the halide by the olefin could occur to give **64** that could then form the product. It is this process of halide displacement by the olefin that the authors favor as the enantiodiscriminating step thus differentiating it from the cationic pathway.

While direct product formation from **65** was regarded as being less likely than the conversion of **65** into **64**, recent results with asymmetric ene-type cyclizations of a 1,6-enyne may indicate that this path should not be ruled out. Mikami and co-workers have found that by varying the reaction conditions, high enantioselectivities (>90% *ee*) can be obtained from both the four-coordinate cationic intermediate (analogous to **64**) and the five-coordinate neutral complex (analogous to **65**) when  $\text{X}$  is trifluoroacetate.<sup>[84]</sup>

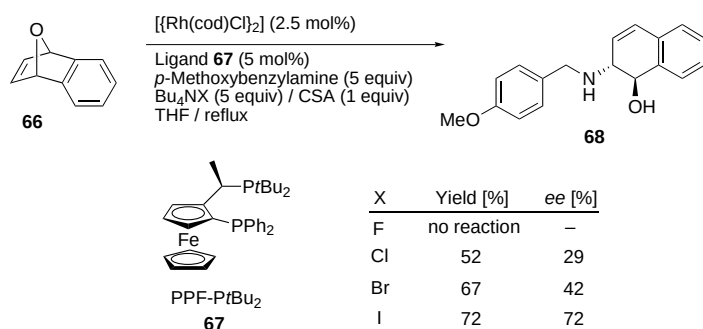
#### 4.1.2. Rhodium and Iridium Catalysis

##### 4.1.2.1. Asymmetric Ring-Opening Reactions

As part of a research program aimed at the development of new asymmetric heteroatom additions to strained olefins,<sup>[85]</sup>

we found a dramatic halide effect in the rhodium-catalyzed asymmetric ring opening (ARO) of oxabenzonorbornadiene **66**. While alcohols and phenols could be used as nucleophiles to induce ring opening in good yield and high *ee* values amines, were problematic. For example, activated amines gave good yield, but poor *ee* values with a catalyst generated in situ from  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$  (cod = cycloocta-1,5-diene) and PPF- $\text{PtBu}_2$  (**67**; PPF = 1-[2-(diphenylphosphanyl)ferrocenyl]-ethane). With the same catalyst, aliphatic amines did not react at all because of catalyst poisoning. This trend in reactivity was also observed in our rhodium-catalyzed ring-opening reactions of vinyl epoxides.<sup>[86]</sup> In an effort to overcome catalyst poisoning, the use of additives was examined. It was found that the combined use of protic and halide additives effectively alleviate the poisoning. The choice of halide was found to be important, fluoride did not result in the formation of product with aliphatic amine nucleophiles. Other halides led to an increase in reactivity according to the trend  $\text{Cl} < \text{Br} < \text{I}$ . The halide additive was found to have a pronounced effect on the enantioselectivity of these transformations (Scheme 33). With *p*-methoxybenzylamine, for example, ligand **67** gives **68** in 29% *ee* with chloride as the halide additive, and 42% with bromide. Addition of iodide gives the best result, producing **68** in 72% *ee*. This value can be improved to 81% if the chloride is first removed by the addition of a silver salt prior to the addition of iodide.

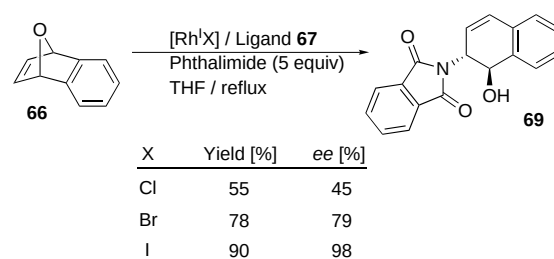
The choice of halide may be used to increase the enantioselectivity with more acidic amine nucleophiles. While the addition of halide or proton additives is not required when activated amines are used, changing the halide ligand on the metal center prior to the addition of reagents leads to a dramatic increase in the enantioselectivity. With phthalimide, for example, the *ee* value increases by 54% to give **69** in 98% *ee* (Scheme 34). This tendency was found to be general for a variety of activated amines.<sup>[87]</sup>



Scheme 33. Effect of halides on aliphatic amine asymmetric-ring opening. CSA = *p*-10-caphorsulfonic acid.

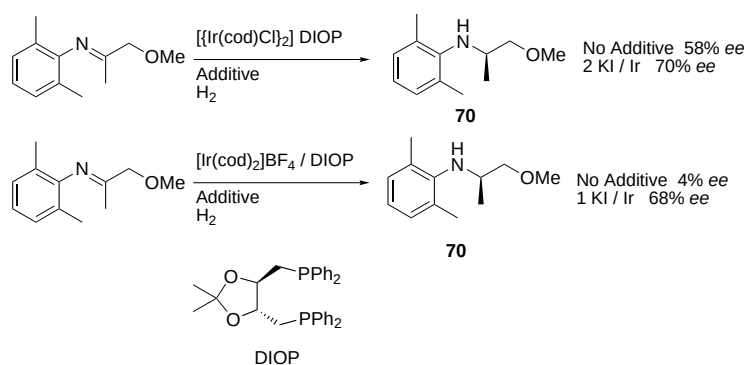
#### 4.1.2.2. Asymmetric Hydrogenations

With the goal of establishing a chiral synthesis for the pesticide metolachlor, an iridium-catalyzed reduction of imines was developed which showed a pronounced halide effect.<sup>[88]</sup> In an initial report, improved yields and enantioselectivities were obtained with the addition of 1–2 equivalents of iodide relative to iridium. For example, when  $[\{\text{Ir}(\text{cod})\text{Cl}\}_2]$



Scheme 34. Effect of halide ligands on activated amine asymmetric ring opening.

and bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolane-4,5-diol (DIOP) are used in the absence of an additive, **70** is obtained in 58% *ee*. When iodide was added, the enantioselectivity improved to 70% (Scheme 35). An even more pronounced halide effect was observed when the cationic  $[\text{Ir}(\text{cod})_2]\text{BF}_4/\text{DIOP}$  catalyst was used. In this case in the absence of an additive **70** was obtained in only 4% *ee*. When iodide was added the enantioselectivity increased to

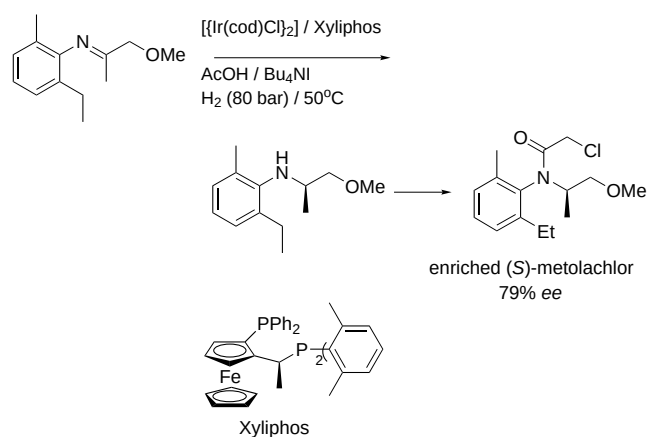


Scheme 35. Halide effects in imine hydrogenations.

68%. It was noted that the addition of iodide afforded better results than chloride or bromide.

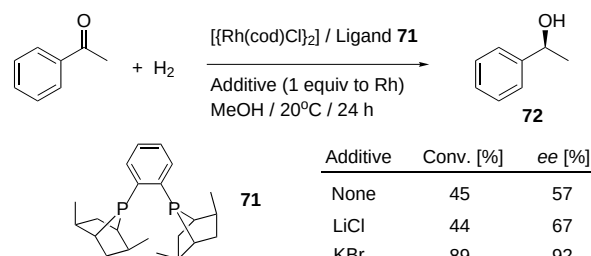
The optimized process for the commercial production of enantiomerically enriched metolachlor operates at a hydrogen pressure of 80 bar at 50 °C with an in situ generated catalyst from  $[\{\text{Ir}(\text{cod})\text{Cl}\}_2]$  and the ferrocenyldiphosphane ligand xyliphos (Scheme 36). For optimal results,  $\text{Bu}_4\text{NI}$  and acetic acid are used which reduce the reaction time 20-fold. Exceptionally low catalyst loading can be used. Typical substrate/catalyst ratios are as high as 1000000:1 and the turnover frequency (TOF) is an outstanding  $350\,000\text{ h}^{-1}$ .<sup>[89]</sup>

Analogous halide effects have been reported with a rhodium-catalyzed hydrogenation of imines<sup>[90]</sup> and, more recently, with ketones.<sup>[91]</sup> Using an in situ generated catalyst from  $[\text{Rh}(\text{nbd})\text{Cl}]_2$  (nbd = norbornadiene), the chiral ligand 1-cyclohexyl-1,2-bis(diphenylphosphanyl)ethane (cycphos)<sup>[92]</sup> and an equivalent of halide, noticeable differences in enantioselectivity were observed. When no additional halide was added, with chloride still as the counter ion, the hydrogenated product was obtained in 67% *ee*. This value increased to 72% *ee* when bromide was added and 79% when iodide was used. The halide effect using a  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]/\text{ligand } \mathbf{71}$  catalyst for the hydrogenation of ketones is more



Scheme 36. Halide effects in the industrial preparation of metolachlor.

pronounced (Scheme 37). In the absence of an additive, acetophenone is hydrogenated to generate alcohol **72** with 45% conversion and 57% *ee* after 24 hours. With one equivalent LiCl (relative to rhodium), **72** is produced with slightly better *ee* value of 67%, in similar conversion under identical conditions. Optimal results were obtained with KBr, with the product formed in 92% *ee* and 85% conversion. No mention was made of the use of iodide. In addition to halides, amine bases were also found to have beneficial effects on both the reactivity and enantioselectivity.



Scheme 37. Effect of halide additives on rhodium-catalyzed ketone hydrogenation.

### 4.1.3. Transition Metal Fluoride Catalysts

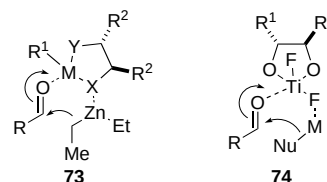
#### 4.1.3.1. Special Properties of the Fluoride Ligand and Fluorine–Metal Complexes

Transition metal fluoro compounds exhibit interesting properties as a result of the fluoride ligand. Experimental evidence indicates that the fluoride ligand confers substantially different properties to the complex compared to the other halide ions. This difference in reactivity has prompted reviews of the chemistry of these complexes<sup>[93]</sup> and their application in asymmetric catalysis.<sup>[94]</sup> Since these reviews are comprehensive, the chemistry of fluoride complexes will be briefly described here and only reactions where the metal–fluoride complex is the active catalyst will be included.

#### 4.1.3.2. Asymmetric Additions to Aldehydes

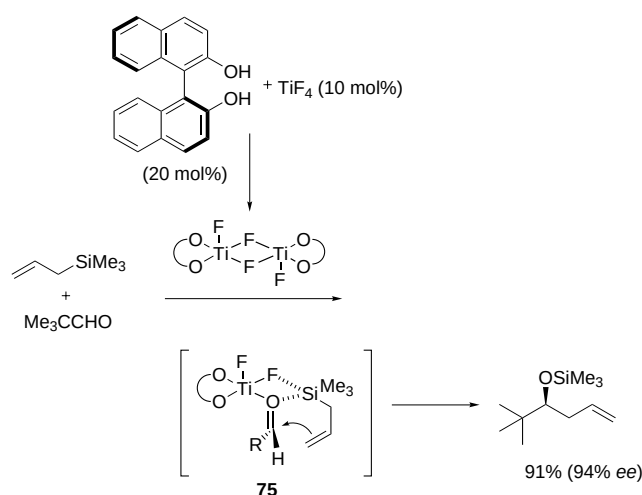
A common feature of successful catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes is that

one of the heteroatom donors in chelate **73** acts as a bridging ligand between the electrophilic metal center and the dialkylzinc species. This complexation not only increases the electrophilicity of the aldehyde and the nucleophilicity of the alkylzinc unit, but also allows the formation of an ordered transition state (Scheme 38).<sup>[95]</sup> Given the propensity for fluoride to act as a bridging ligand, if complexes such as **74** could be formed, high selectivities could be anticipated.<sup>[96]</sup>



Scheme 38. Bridging structures in the asymmetric addition to aldehydes.

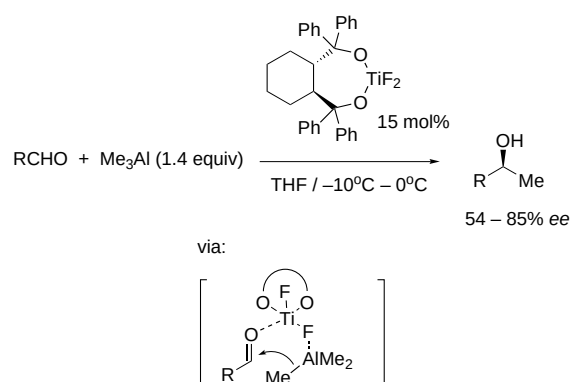
Carreira and Gauthier described a titanium–fluoride catalyst for the addition of allyltrimethylsilane to aldehydes. Using a catalyst derived from TiF<sub>4</sub> and 2,2'-dihydroxy-1,1'-binaphthyl (BINOL), enantioselectivities up to 94% have been obtained (Scheme 39).<sup>[97]</sup> The importance of fluoride as a



Scheme 39. Asymmetric allylsilation of aldehydes.

ligand in this reaction is demonstrated by the fact that complexes prepared with TiCl<sub>4</sub> and TiBr<sub>4</sub> are not active. This pronounced difference in reactivity was proposed to stem from the strong electron-withdrawing nature of the fluoride ligands and the strong Ti–F bond. This effect would result in the Ti center becoming more Lewis acidic and hence further activate the aldehyde to attack. Furthermore, the bridging ability of fluoride was proposed by Duthaler<sup>[84]</sup> to activate the silane as a nucleophile<sup>[98]</sup> and increase the facial selectivity through the formation of adduct **75**.

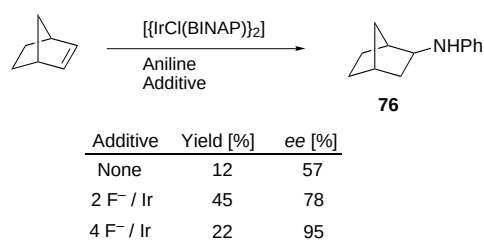
Another example illustrating this concept, described by Carreira and Pagenkopf, involves the enantioselective addition of trimethylaluminum to aldehydes in up to 85% *ee* (Scheme 40).<sup>[99]</sup> Given the affinity of aluminum for fluoride,<sup>[100]</sup> the formation of a fluoride bridge is again invoked to explain the reactivity.



Scheme 40. Asymmetric addition of trimethylaluminum to aldehydes.

#### 4.1.3.3. Asymmetric Hydroaminations

Togni and co-workers have also uncovered a dramatic halide effect in an asymmetric iridium-catalyzed hydroamination reaction where the use of fluoride was found to produce the optimal results.<sup>[101]</sup> The addition of four equivalents of fluoride gave **76** in 95% *ee* (Scheme 41). In the absence of fluoride the enantioselectivity was only 57% *ee*. It was mentioned that the use of chloride, bromide, or iodide in place of fluoride has either no effect or only detrimental effects on activity and enantioselectivity. It was proposed that the good  $\pi$ -donating ability of fluoride in addition to its tendency to form hydrogen bridges could enhance the ability of iridium(i) to undergo N–H insertion.

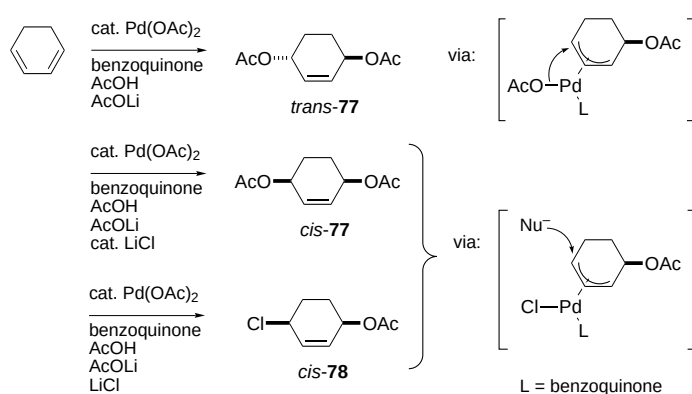


Scheme 41. Halide effects in iridium-catalyzed asymmetric hydroamination.

## 4.2. Halide Effects in Achiral Catalytic Processes

### 4.2.1. Diverting Reaction Pathways Through Coordination-Site Occupation

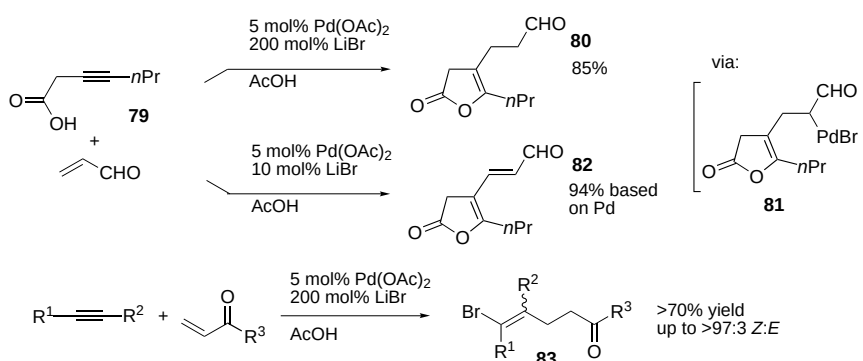
Bäckvall et al. have reported that 1,3-dienes can be regio- and stereoselectively functionalized at the 1,4-positions by palladium-catalyzed transformations (Scheme 42).<sup>[102]</sup> The first step in these reactions involves the *trans*-acetoxypalladation of one of the olefins to generate a  $\pi$ -allyl intermediate with the second olefin. Subsequent reaction of this intermediate was found to be highly sensitive to the relative amounts of lithium acetate and lithium chloride in the reaction mixture. When LiOAc is used as the nucleophile in the



Scheme 42. Effect of halides on the acetoxypalladation reaction.

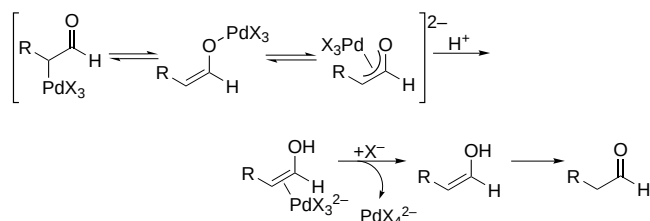
absence of LiCl, *trans*-**77** is produced by an intramolecular delivery of the acetate nucleophile from the palladium. When catalytic amounts of LiCl are added, the stereochemistry of the second acetate delivery is reversed. The authors propose that chloride ions bind preferentially to the palladium thus occupying the coordination site previously available to the acetate. Since intramolecular delivery of the acetate is blocked, intermolecular nucleophilic attack occurs with inversion to generate *cis*-**77**. When an excess of LiCl is used, *cis*-**78** becomes the product as a result of intermolecular nucleophilic attack by the chloride ion. In each of these cases, high selectivity for the 1,4-addition product is observed.<sup>[103]</sup> This inversion of stereochemistry because of the presence of halide ions was also observed in palladium-catalyzed 1,4-oxylactonizations.<sup>[104]</sup>

Lu and co-workers have reported that the use of excess halides can alter the reaction outcome of Heck-type couplings with  $\alpha,\beta$  unsaturated carbonyl compounds. The typical pathway for Heck reactions involves a carbopalladation step followed by  $\beta$ -hydride elimination. When excess halide is present, the  $\beta$ -hydride elimination step is suppressed allowing protonolysis of the palladium enolate to occur in acidic media.<sup>[105]</sup> For example, when **79** is treated with acrolein in the presence of catalytic amounts of [Pd(OAc)<sub>2</sub>] and 200 mol % LiBr, **80** is generated exclusively (Scheme 43). This product arises from the oxypalladation of the alkyne followed by carbopalladation of the acrolein to generate intermediate **81**. In the presence of 200 mol % LiBr,  $\beta$ -hydride elimination was effectively inhibited allowing protonolysis to occur. When

Scheme 43. Effect of excess halide on  $\beta$ -hydride suppression.

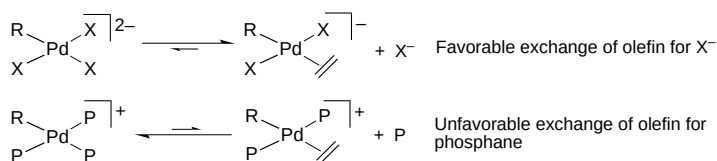
only 10 mol % LiBr is used, the typical Heck-type product **82** is formed by the standard  $\beta$ -hydride elimination pathway in 94% yield based on Pd.<sup>[106]</sup> An analogous reaction with alkynes and acrylates also allows selective protonolysis of the palladium-enolate intermediate to give **83**. This process has also been used to produce (*E,Z*)- $\gamma,\delta$  unsaturated carbonyl compounds.<sup>[107]</sup>

The effect of the nature of the anion was studied and it was found that LiOAc, LiF, and LiClO<sub>4</sub> all afforded the normal Heck-type product resulting from  $\beta$ -hydride elimination. LiCl, LiBr, and LiI, on the other hand, only gave the 1,4-addition products arising from protonation. Lu proposed that the protonation process is facilitated by three factors.<sup>[105]</sup> First, the presence of an excess of halide diminishes the  $\beta$ -elimination by occupation of the free coordination site. Second, the electron donation from the halide to the Pd center results in a highly polarized Pd–C bond which increases its susceptibility to protonation. Third, the palladium enolate is in equilibrium with a  $\pi$ -oxoallylpalladium form (Scheme 44) and the ionic nature of the Pd–O bond will facilitate protonation.



Scheme 44. Mechanism of halide suppression of  $\beta$ -hydride elimination.

Lu also drew attention to another important aspect of the use of halide ligands to prevent  $\beta$ -elimination. He noted that the same result cannot be achieved with the use of excess phosphane ligands since the addition of phosphanes shuts down the reaction by blocking the coordination of the olefin. The advantage of using halide ligands may result from the facile ligand exchange from a halide to an olefin while exchange of a phosphane for an olefin is very slow (Scheme 45).



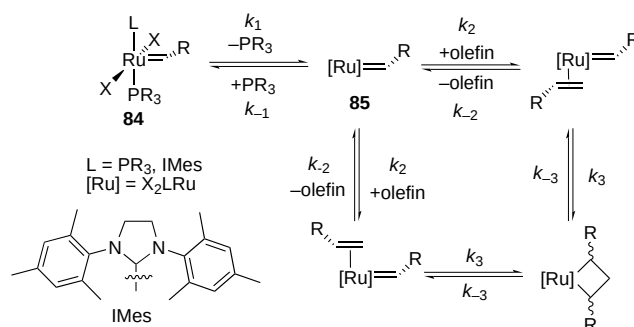
Scheme 45. Halide versus phosphane ligands and olefin coordination.

#### 4.2.2. Olefin Metathesis

The past several years have seen a revolution in the field of olefin metathesis, largely a result of the discovery and application of air-stable catalysts.<sup>[108]</sup> The ruthenium catalysts developed by Grubbs and co-workers have found particularly widespread application, and the “first generation” bisphosphane complex **84** (L = PCy<sub>3</sub>, R = Cy, X = Cl),<sup>[109]</sup> has recently been followed by a more reactive, second-generation com-

plex **84** (L = *N,N'*-bis(2,4,6-trimethylphenyl)imidazolidine-2-yl (IMes), R = Cy, X = Cl).<sup>[110]</sup> Intense effort has been devoted to the mechanistic study of these reactions, with the hope of enabling the development of even more highly reactive catalysts. Recent work has shed light on the effect of the various ligands and has revealed the presence of a large halide effect for both generations of the Ru catalysts.

To probe the effect of ligands on the ruthenium metathesis catalysts [L(PR<sub>3</sub>)(X)<sub>2</sub>Ru=CHR], a variety of different complexes **84** were prepared and each of the variables, L, R, and X, was found to influence the catalytic activity.<sup>[111]</sup> The halide ligands, in particular, were found to exert a dramatic effect on the phosphane dissociation required for catalyst initiation and generation of the propagating catalyst species **85** (Scheme 46). Changing the X ligands from chloride to iodide resulted in a 250-fold increase in phosphane dissociation (*k*<sub>1</sub>). Changing from chloride to bromide also increased initiation, albeit by only a threefold difference. Grubbs attributed these differences in initiation to the relative size of the halides.<sup>[111]</sup> Since dissociation of PR<sub>3</sub> will be favored by an increase in steric congestion at the metal, the larger halides will favor this process.



Scheme 46. Halide effects in olefin metathesis.

While the diiodo complexes show the fastest initiation, their olefin metathesis activities are comparable or lower than that of the dichloride analogues despite the fact that the propagating species **85** is present in higher concentration. This result indicates that the propagating species **85** is significantly less active when X = I than when X = Cl. The difference in reactivity has been attributed to the ratio of *k*<sub>-1</sub> to *k*<sub>2</sub>. In both the first and second generation ruthenium catalysts, the change from the diiodide species to the dichloride resulted in a 100-fold increase in *k*<sub>-1</sub>/*k*<sub>2</sub>. While the reasons for this shift are not clearly understood, it has been suggested that olefin coordination may require a *trans* to *cis* isomerization of the X ligands.<sup>[112]</sup> This isomerization could be less favorable with large X ligands and result in a decrease in *k*<sub>2</sub> for the diiodo catalysts.

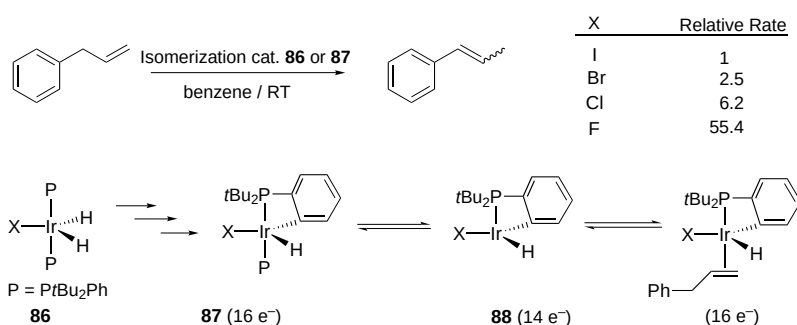
#### 4.2.3. Olefin Isomerization

Caulton and Cooper have uncovered a significant halide effect in studies aimed at identifying the active olefin-isomerization catalyst when **86** is used as the catalyst precursor.<sup>[113]</sup> It was found that **87** could be isolated from the reaction and that

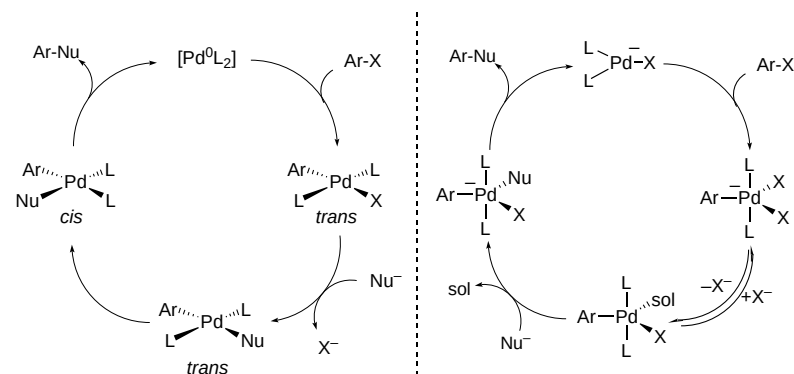
**87** was also an active isomerization catalyst. It was determined that catalysts with better  $\pi$ -donating ligands were the most reactive and that the catalyst with  $X = F$  was most reactive (Scheme 47). The authors propose that this trend indicates that the rate-determining step involves a transition to a more highly unsaturated species **88**. Since the equilibrium constant for such a process would be highly influenced by the presence of a  $\pi$ -donating ligand, such a ligand would make the process more favorable and thus increase the concentration of the active 14-electron complex. On the contrary, if the rate-determining step would have involved the generation of a six-coordinate 18-electron  $d^6$  species by coordination of the olefin directly to **87**, the opposite trend in dependence on the halide ligand would have been expected.

#### 4.2.4. Palladium-Catalyzed Coupling Reactions

Palladium(0) catalysts are commonly used in a wide range of transformations including allylic substitution, aryl amination, Heck reactions, and Suzuki couplings. A typical catalyst precursor is  $[Pd(PPh_3)_4]$  where the active catalyst is the coordinatively unsaturated 14-electron  $[Pd(PPh_3)_2]$ . Through the study of stoichiometric reactions, the reaction mechanism for palladium-catalyzed coupling reactions was established to include oxidative insertion, transmetalation, isomerization, and reductive elimination steps (Scheme 48, mechanism 1 in the absence of free halide). Even though evidence for each of the individual steps was obtained, proof that they were operative within the catalytic cycle was not demonstrated.



Scheme 47. Effect of the halide ligand on the rate of olefin isomerization.



Scheme 48. Proposed mechanisms for palladium-catalyzed cross-coupling reactions. Left: mechanism 1, cross-coupling without free halide or in the presence of excess phosphane. Right: mechanism 2 cross-coupling in presence of free halide.

Indeed, evidence revealed that this assumption was incorrect, at least in certain cases. For example, kinetic work indicated that the catalytic process for the entire cycle was faster than the substitution and reductive elimination processes that were supposed to lie within the catalytic cycle.<sup>[114]</sup> Evidence that another mechanism may be operating was obtained by Amatore, Azzabi, and Jutand<sup>[49]</sup> when it was determined that the rate of reaction of palladium(0) species generated by electrochemical reduction of  $[PdX_2(PPh_3)_2]$  with PhI depended on the nature of the halide in the  $Pd^{II}$  precursor (see Section 3.7).

Further mechanistic work by Amatore and Jutand has produced a more accurate description of the catalytic cycle involved in palladium-catalyzed coupling reactions.<sup>[49]</sup> While the earlier proposed mechanism 1 may still operate under conditions free of halides (or acetate ions) or when an excess of phosphane is present (as when the catalyst precursor is  $[Pd(PPh_3)_4]$ ), a new mechanism incorporating the newly obtained mechanistic information was put forward. Furthermore, even when mechanism 1 (Scheme 48) may operate early on in the reaction, if there is an accumulation of halide in the reaction mixture because of the consumption of the aryl halide, mechanism 2 will become operative and gradually become the predominant pathway for the reaction (Scheme 48). Important conclusions include that when such anionic ligands are present,  $[Pd(PPh_3)_2]$  will not be present in solution but will be replaced by the  $[Pd(PPh_3)_2X]^-$  ion. In addition, the halide ligand will be intimately involved in all of the key processes of the catalytic cycle and should therefore not be ignored.

## 5. Outlook

It is readily apparent that much more mechanistic work is required to fully understand the processes involved in halide effects, especially in the field of asymmetric catalysis. A better understanding of the processes would greatly assist chemists in the application of halide effects towards the development of new transformations.

Halides are much more than innocent ancillary ligands. Rather, the presence of the metal-halide group should be viewed as a highly valuable functionality that can allow fine-tuning of the catalyst's properties. The subtle changes imparted by varying the halide are often predictable and can be synthetically useful. The experimental evidence behind the notion of the metal-halide moiety as a *tunable functionality* on the catalyst species should be of considerable value for those working within the field of transition metal catalysis.

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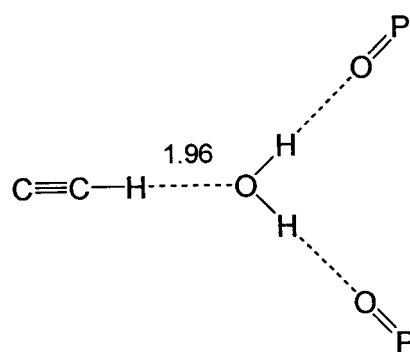
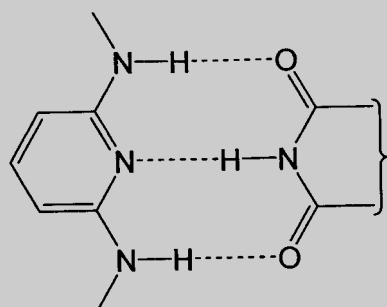
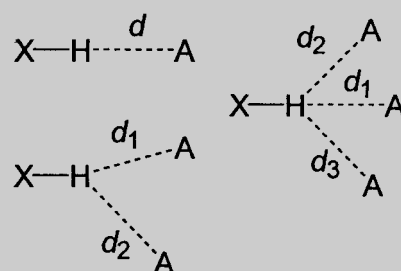
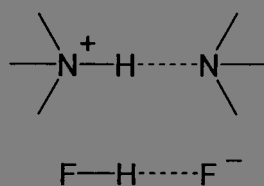
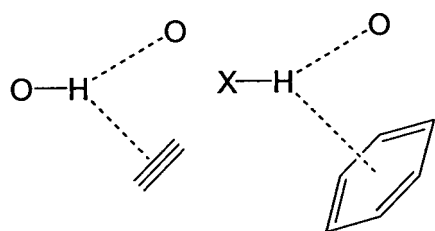
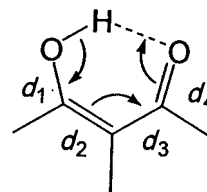
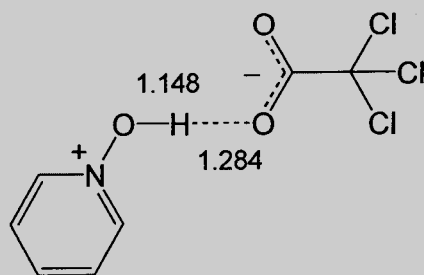
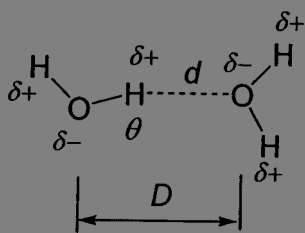
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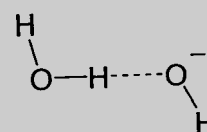
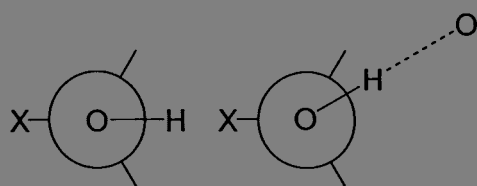
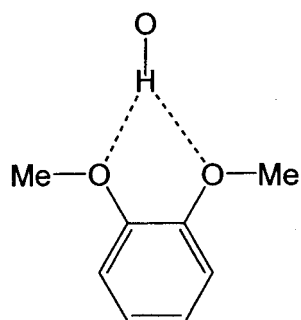
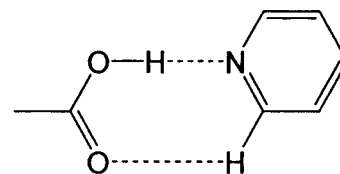
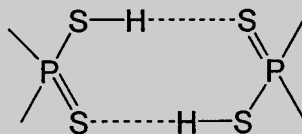
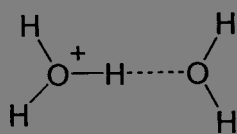
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# The whole palette of hydrogen bonds



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# The Hydrogen Bond in the Solid State

Thomas Steiner\*

*In memory of Jan Kroon*

The hydrogen bond is the most important of all directional intermolecular interactions. It is operative in determining molecular conformation, molecular aggregation, and the function of a vast number of chemical systems ranging from inorganic to biological. Research into hydrogen bonds experienced a stagnant period in the 1980s, but re-opened around 1990, and has been in rapid development since then. In terms of modern concepts, the hydrogen bond is understood as a very broad phenomenon, and it is accepted that there are open borders to other

effects. There are dozens of different types of  $X-H\cdots A$  hydrogen bonds that occur commonly in the condensed phases, and in addition there are innumerable less common ones. Dissociation energies span more than two orders of magnitude (about  $0.2-40 \text{ kcal mol}^{-1}$ ). Within this range, the nature of the interaction is not constant, but its electrostatic, covalent, and dispersion contributions vary in their relative weights. The hydrogen bond has broad transition regions that merge continuously with the covalent bond, the van der Waals interaction,

the ionic interaction, and also the cation- $\pi$  interaction. All hydrogen bonds can be considered as incipient proton transfer reactions, and for strong hydrogen bonds, this reaction can be in a very advanced state. In this review, a coherent survey is given on all these matters.

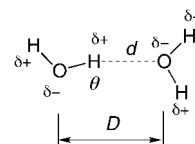
**Keywords:** donor-acceptor systems • electrostatic interactions • hydrogen bonds • noncovalent interactions • proton transfer

## 1. Introduction

The hydrogen bond was discovered almost 100 years ago,<sup>[1]</sup> but still is a topic of vital scientific research. The reason for this long-lasting interest lies in the eminent importance of hydrogen bonds for the structure, function, and dynamics of a vast number of chemical systems, which range from inorganic to biological chemistry. The scientific branches involved are very diverse, and one may include mineralogy, material science, general inorganic and organic chemistry, supramolecular chemistry, biochemistry, molecular medicine, and pharmacy. The ongoing developments in all these fields keep research into hydrogen bonds developing in parallel. In recent years in particular, hydrogen-bond research has strongly expanded in depth as well as in breadth, new concepts have been established, and the complexity of the phenomena considered has increased dramatically. This review is intended to give a coherent survey of the state of the art, with a focus on

the structure in the solid state, and with weight put mainly on the fundamental aspects. Numerous books<sup>[2-9]</sup> and reviews on the subject have appeared earlier, so a historical outline is not necessary. Much of the published numerical material is somewhat outdated and, therefore, this review contains some numerical data that have been newly retrieved from the most relevant structural database, the Cambridge Structural Database (CSD).<sup>[10]</sup>

It is pertinent to recall here the earlier “classical” view on hydrogen bonding. One may consider the directional interaction between water molecules as the prototype of all hydrogen bonds (Scheme 1, definitions of geometric parameters are also included). The large difference in electronegativity between the H and O atoms makes the O-H bonds of a water molecule inherently polar, with partial atomic charges of around  $+0.4$  on each H atom and  $-0.8$  on the O atom. Neighboring water molecules orient in such a way that local dipoles  $O^{\delta-}-H^{\delta+}$  point at negative partial charges  $O^{\delta-}$ , that is, at the electron lone pairs of the filled p orbitals. In the resulting



Scheme 1. Prototype of a hydrogen bond: the water dimer. Definitions of geometrical parameters:  $d = H\cdots O$  distance,  $D = O\cdots O$  distance,  $\theta = O-H\cdots O$  angle.

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O–H $\cdots$ |O interaction, the intermolecular distance is shortened by around 1 Å compared to the sum of the van der Waals radii for the H and O atoms<sup>[11]</sup> (1 Å = 100 pm), which indicates there is substantial overlap of electron orbitals to form a three-center four-electron bond. Despite significant charge transfer in the hydrogen bond, the total interaction is dominantly electrostatic, which leads to pronounced flexibility in the bond length and angle. The dissociation energy is around 3–5 kcal mol<sup>–1</sup>.

This brief outline of the hydrogen bond between water molecules can be extended, with only minor modifications, to analogous interactions X–H $\cdots$ A formed by strongly polar groups X $\delta^-$ –H $\delta^+$  on one side, and atoms A $\delta^-$  on the other (X = O, N, halogen; A = O, N, S, halide, etc.). Many aspects of hydrogen bonds in structural chemistry and structural biology can be readily explained at this level, and it is certainly the relative success of these views that made them dominate the perception of the hydrogen bond for decades. This dominance has been so strong in some periods that research on hydrogen bonds differing too much from the one between water molecules was effectively impeded.<sup>[8]</sup>

Today, it is known that the hydrogen bond is a much broader phenomenon than sketched above. What can be called the “classical hydrogen bond” is just one among many—a very abundant and important one, though. We know of hydrogen bonds that are so strong that they resemble covalent bonds in most of their properties, and we know of others that are so weak that they can hardly be distinguished from van der Waals interactions. In fact, the phenomenon has continuous transition regions to such different effects as the covalent bond, the purely ionic, the cation– $\pi$ , and the van der Waals interaction. The electrostatic dominance of the hydrogen bond is true only for some of the occurring configurations, whereas for others it is not. The H $\cdots$ A distance is not in all hydrogen bonds shorter than the sum of the van der Waals radii. For an X–H group to be able to form hydrogen bonds, X does not need to be “very electronegative”, it is only necessary that X–H is at least slightly polar. This requirement includes groups such as C–H, P–H, and some metal hydrides. X–H groups of reverse polarity, X $\delta^+$ –H $\delta^-$ , can form directional interactions that parallel hydrogen bonds (but one can argue that they should not be called so). Also, the counterpart A does not need to be a

particularly electronegative atom or an anion, but only has to supply a sterically accessible concentration of negative charge. The energy range for dissociation of hydrogen bonds covers more than two factors of ten, about 0.2 to 40 kcal mol<sup>–1</sup>, and the possible functions of a particular type of hydrogen bond depend on its location on this scale. These issues shall all be discussed in the following sections.

For space reasons, it will not be possible to cover all aspects of hydrogen bonding equally well. Therefore, some important fields, for which recent guiding reviews are available, will not be discussed in great length. One example is the role of hydrogen bonds in molecular recognition patterns (“supramolecular synthons”),<sup>[12]</sup> and the use of suitably robust motifs for the construction of crystalline architectures with desired properties (“crystal engineering”).<sup>[13, 14]</sup> This area includes the interplay of hydrogen bonds with other intermolecular forces, with whole arrays of such forces, and hierarchies within such an interplay. The reader interested in this complex field is referred to the articles of Desiraju,<sup>[12, 13]</sup> Leiserowitz et al.,<sup>[15]</sup> and others.<sup>[16]</sup> A further topic which could not be covered here is the symbolic description of hydrogen bond networks using tools of graph theory,<sup>[17]</sup> in particular the “graph set analysis”.<sup>[18]</sup> An excellent guiding review is also available in this case.<sup>[19]</sup> For hydrogen bonding in biological structures, the interested reader is referred to the book of Jeffrey and Saenger,<sup>[5]</sup> and for theoretical aspects to the book of Scheiner<sup>[7]</sup> as well as other recent reviews.<sup>[20]</sup> Results obtained with experimental methods other than diffraction will be touched upon only briefly, and will possibly leave some readers dissatisfied. The role of hydrogen bonding in special systems will not be discussed at all, simply because there are too many of them.

## 2. Fundamentals

### 2.1. Definition of the Hydrogen Bond

Before discussing the hydrogen bond itself, the matter of hydrogen bond definitions must be addressed. This is an important point, because definitions of terms often limit entire fields. It is, also, a problematic point because very different hydrogen bond definitions have been made, and part



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of the literature relies quite uncritically on the validity (or the value) of the particular definition that is adhered to.

Time has shown that only very general and flexible definitions of the term “hydrogen bond” can do justice to the complexity and chemical variability of the observed phenomena, and include the strongest as well as the weakest species of the family, and inter- as well as intramolecular interactions. A far-sighted early definition is that of Pimentel and McClellan, who essentially wrote that “...a hydrogen bond exists if 1) there is evidence of a bond, and 2) there is evidence that this bond sterically involves a hydrogen atom already bonded to another atom”.<sup>[2]</sup> This definition leaves the chemical nature of the participants, including their polarities and net charges, unspecified. No restriction is made on the interaction geometry except that the hydrogen atom must be somehow “involved”. The crucial requirement is the existence of a “bond”, which is itself not easy to define. The methods to test experimentally if requirements 1 and 2 are fulfilled are limited. For crystalline compounds, it is easy to see with diffraction experiments whether an H atom is involved, but it is difficult to guarantee that a given contact is actually “bonding”.

A drawback of the Pimentel and McClellan definition is that in the strict sense it includes pure van der Waals contacts (which can be clearly “bonding”, with energies of several tenths of a kcal mol<sup>-1</sup>), and it also includes three-center two-electron interactions where electrons of an X–H bond are donated sideways to an electron-deficient center (“agostic interaction”). From a modern viewpoint, it seems advisable to modify point 2, such as by requiring that X–H acts as a proton (not electron) donor. Therefore, the following definition is proposed:

*An X–H...A interaction is called a “hydrogen bond”, if 1. it constitutes a local bond, and 2. X–H acts as proton donor to A.*

The second requirement is related to the acid/base properties of X–H and A, and has the chemical implication that a hydrogen bond can at least in principle be understood as an incipient proton-transfer reaction from X–H to A. It excludes, for example, pure van der Waals contacts, agostic interactions, so-called “inverse hydrogen bonds” (see Section 8), and B–H–B bridges. As a matter of fact, point 2 should be interpreted liberally enough to include symmetric hydrogen bonds X–H...X, where donor and acceptor cannot be distinguished. The direction of formal or real electron transfer in a hydrogen bond is reverse to the direction of proton donation.

Apart from general chemical definitions, there are many specialized definitions of hydrogen bonds that are based on certain sets of properties that can be studied with a particular technique. For example, hydrogen bonds have been defined on the basis of interaction geometries in crystal structures (short distances, fairly “linear angles”  $\theta$ ), certain effects in IR absorption spectra (red-shift and intensification of  $\nu_{\text{XH}}$ , etc.), or certain properties of experimental electron density distributions (existence of a “bond critical point” between H and A, with numerical parameters within certain ranges). All such definitions are closely tied to a specific technique, and may be

quite useful in the regime accessible to it. Nevertheless, they are more or less useless outside that regime, and many a misunderstanding in the hydrogen bond literature has been caused by applying such definitions outside their region of applicability.

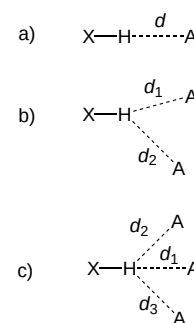
The practical scientist often requires a technical definition, and automated data treatment procedures for identifying hydrogen bonds cannot be done without. It is not within the scope of this article to discuss any set of threshold values that a “hydrogen bond” must pass in any particular type of technical definition. It is only mentioned that the “van der Waals cutoff” definition<sup>[21]</sup> for identifying hydrogen bonds on a structural basis (requiring that the H...A distance is substantially shorter than the sum of the van der Waals radii of H and A) is far too restrictive and should no longer be applied.<sup>[5, 6, 8]</sup> If distance cutoff limits must be used, X–H...A interactions with H...A distances up to 3.0 or even 3.2 Å should be considered as potentially hydrogen bonding.<sup>[6]</sup> An angular cutoff can be set at  $>90^\circ$  or, somewhat more conservatively, at  $>110^\circ$ . A necessary geometric criterion for hydrogen bonding is a positive directionality preference, that is, linear X–H...A angles must be statistically favored over bent ones (this is a consequence of point 2 of the above definition).<sup>[22]</sup>

## 2.2. Further Terminology

A large part of the terminology concerning hydrogen bonds is not uniformly used in the literature, and still today, terminological discrepancies lead to misunderstanding between different authors. Therefore, some of the technical terms used in this review need to be explicitly defined.

In a hydrogen bond X–H...A, the group X–H is called the *donor* and A is called the *acceptor* (short for “proton donor” and “proton acceptor”, respectively). Some authors prefer the reverse nomenclature (X–H = electron *acceptor*, Y = electron *donor*), which is equally justified.

In a simple hydrogen bond, the donor interacts with one acceptor (Scheme 2a). Since the hydrogen bond has a long range, a donor can interact with two and three acceptors simultaneously (Scheme 2b, c). Hydrogen bonds with more than three acceptors are possible in principle, but are only rarely found in practice because they require very high spatial densities of acceptors. The terms “bifurcated” and “trifurcated” are commonly used to describe the arrangements in Scheme 2b and c, respectively. The term “two-centered” hydrogen bond is an alternative descriptor for X–H...A (Scheme 2a) where the H-atom is bonded to *two* other atoms, and is itself not



Scheme 2. Different types of hydrogen bridges. a) Normal hydrogen bond with one acceptor. b) Bifurcated hydrogen bond; if the two H...A separations are distinctly different, the shorter interaction is called major component, and the longer one the minor component of the bifurcated bond. c) Trifurcated hydrogen bond.

counted as a center. Consequently, the arrangements in Scheme 2b and 2c may be called “three-” and “four-centered” hydrogen bonds, respectively.<sup>[5, 6]</sup> This terminology is logical, but leads to confusion from the point of view of regarding hydrogen bonds  $\text{O}-\text{H}\cdots\text{O}$  as “three-center four-electron” interactions, where the H-atom is counted as a center. A bifurcated hydrogen bond (Scheme 2b) is then termed “three-centered”, but also represents a “four-center six-electron” interaction. To avoid such ambiguities, the older term “bifurcated” is used here.

There is particular confusion concerning the terms *attractive* and *repulsive*. Some authors use these terms to characterize forces, and others to characterize energies. In the latter case, an “attractive interaction” is taken as a synonym for “bonding interaction”, that is, one that requires the input of energy to be broken. Following well-founded recommendations,<sup>[23]</sup> the terms “attractive” and “repulsive” are used here exclusively to describe forces. Negative and positive bond energies are indicated by the terms “stabilizing” (or “bonding”) and “destabilizing”, respectively. The schematic hydrogen bond potential in Figure 1 shows that a stabilizing interaction (that is, with  $E < 0$ ) is associated with a repulsive force if it is shorter than the equilibrium distance (see figure legend for further details).<sup>[8]</sup>

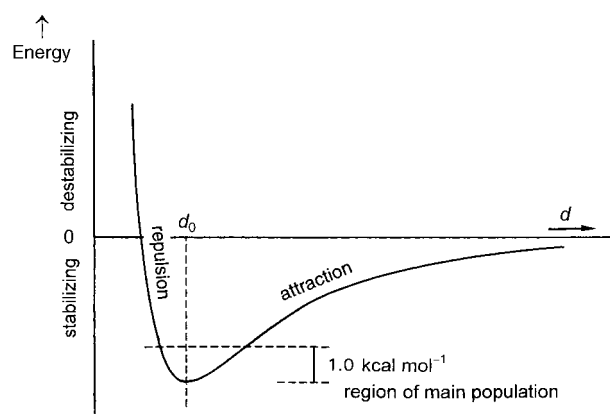


Figure 1. Schematic representation of a typical hydrogen bond potential.<sup>[8]</sup> A hydrogen bond length differing from  $d_0$  implies a force towards a geometry of lower energy, that is, by attraction if  $d > d_0$  and repulsion if  $d < d_0$ . Note that the interaction can at the same time be “stabilizing” (or “bonding”) and “repulsive”! The distortions from  $d_0$  occurring in practice are limited by the energy penalties that have to be paid, and in crystals, only a few hydrogen bonds have energies differing by more than  $1 \text{ kcal mol}^{-1}$  from optimum.

Hydrogen bonds are sometimes called “nonbonded interactions”. At least to this author, this appears a contradiction in terms which should be avoided.

### 2.3. Constituent Interactions

The hydrogen bond is a complex interaction composed of several constituents that are different in their natures.<sup>[6, 7]</sup> Most popular are partitioning modes that essentially follow those used by Morokuma.<sup>[24]</sup> The total energy of a hydrogen bond ( $E_{\text{tot}}$ ) is split into contributions from electrostatics ( $E_{\text{el}}$ ),

polarization ( $E_{\text{pol}}$ ), charge transfer ( $E_{\text{ct}}$ ), dispersion ( $E_{\text{disp}}$ ), and exchange repulsion ( $E_{\text{er}}$ ), somewhat different, but still related, partitioning schemes are also in use. The distance and angular characteristics of these constituents are very different. The electrostatic term is directional and of long range (diminishing only slowly as  $-r^{-3}$  for dipole–dipole and as  $-r^{-2}$  for dipole–monopole interactions). Polarization decreases faster ( $-r^{-4}$ ) and the charge-transfer term decreases even faster, approximately following  $e^{-r}$ . According to natural bond orbital analysis,<sup>[25]</sup> charge transfer occurs from an electron lone pair of A to an antibonding orbital of X–H, that is  $n_{\text{A}} \rightarrow \sigma_{\text{XH}}^*$ . The dispersion term is isotropic with a distance dependence of  $-r^{-6}$ . The exchange repulsion term increases sharply with reducing distance (as  $+r^{-12}$ ). The dispersion and exchange repulsion terms are often combined into an isotropic “van der Waals” contribution that is approximately described by the well-known Lennard–Jones potential ( $E_{\text{vdW}} \sim A r^{-12} - B r^{-6}$ ). Depending on the particular chemical donor–acceptor combination, and the details of the contact geometry, all these terms contribute with different weights. It cannot be globally stated that the hydrogen bond as such is dominated by this or that term in any case.

Some general conclusions can be drawn from the overall distance characteristics. In particular, it is important that of all the constituents, the electrostatic contribution reduces slowest with increasing distance. The hydrogen bond potential for any particular donor–acceptor combination (Figure 1) is, therefore, dominated by electrostatics at long distances, even if charge transfer plays an important role at optimal geometry. Elongation of a hydrogen bond from optimal geometry *always* makes it more electrostatic in nature.

In “normal” hydrogen bonds  $E_{\text{el}}$  is the largest term, but a certain charge-transfer contribution is also present. The van der Waals terms too are always present, and for the weakest kinds of hydrogen bonds dispersion may contribute as much as electrostatics to the total bond energy. Purely “electrostatic plus van der Waals” models can be quite successful despite their simplicity for hydrogen bonds of weak to intermediate strengths.<sup>[26]</sup> Such simple models fail for the strongest types of hydrogen bonds, for which their quasi-covalent nature has to be fully considered (see Section 7).

### 2.4. Energies

The energy of hydrogen bonds in the solid state cannot be directly measured, and this circumstance leaves open questions in many structural studies. Computational chemistry, on the other hand, produces results on hydrogen bond energies at an inflationary rate,<sup>[7, 20]</sup> many obtained at high levels of theory and even more in rather routine calculations using black-box methods. Theoretical studies are not the topic of the present review, but an idea of typical results can be gained from the collection of calculated values listed in Table 1.<sup>[27]</sup> It appears that hydrogen bond energies cover more than two orders of magnitude, about  $-0.2$  to  $-40 \text{ kcal mol}^{-1}$ . On a logarithmic scale, the bond energy of the water dimer is roughly in the middle.



Table 1. Calculated hydrogen bond energies (kcal mol<sup>-1</sup>) in some gas-phase dimers.<sup>[a]</sup>

| Dimer                                              | Energy             | Ref.      |
|----------------------------------------------------|--------------------|-----------|
| [F–H–F] <sup>+</sup>                               | 39                 | [27a]     |
| [H <sub>2</sub> O–H–OH] <sup>+</sup>               | 33                 | [27b]     |
| [H <sub>3</sub> N–H–NH <sub>3</sub> ] <sup>+</sup> | 24                 | [27b]     |
| [HO–H–OH] <sup>+</sup>                             | 23                 | [27a]     |
| NH <sub>4</sub> <sup>+</sup> ⋯OH <sub>2</sub>      | 19                 | [27c]     |
| NH <sub>4</sub> <sup>+</sup> ⋯Bz                   | 17                 | [27d]     |
| HOH⋯Cl <sup>−</sup>                                | 13.5               | [27c]     |
| O=C–OH⋯O=C–OH                                      | 7.4                | [27e]     |
| HOH⋯OH <sub>2</sub>                                | 4.7; 5.0           | [27f,g]   |
| N≡C–H⋯OH <sub>2</sub>                              | 3.8                | [27h]     |
| HOH⋯Bz                                             | 3.2                | [27i]     |
| F <sub>3</sub> C–H⋯OH <sub>2</sub>                 | 3.1                | [27j]     |
| Me–OH⋯Bz                                           | 2.8                | [27k]     |
| F <sub>2</sub> HC–H⋯OH <sub>2</sub>                | 2.1; 2.5           | [27f,j]   |
| NH <sub>3</sub> ⋯Bz                                | 2.2                | [27i]     |
| HC≡CH⋯OH <sub>2</sub>                              | 2.2                | [27h]     |
| CH <sub>4</sub> ⋯Bz                                | 1.4                | [27i]     |
| PH <sub>3</sub> –H⋯OH <sub>2</sub>                 | 1.3                | [27f,j]   |
| HC≡CH⋯C≡CH <sup>−</sup>                            | 1.2                | [27l]     |
| HSH⋯SH <sub>2</sub>                                | 1.1                | [27m]     |
| H <sub>2</sub> C=CH <sub>2</sub> ⋯OH <sub>2</sub>  | 1.0                | [27l]     |
| CH <sub>4</sub> ⋯OH <sub>2</sub>                   | 0.3; 0.5; 0.6; 0.8 | [27f,n–p] |
| C=CH <sub>2</sub> ⋯C=C                             | 0.5                | [27l]     |
| CH <sub>4</sub> ⋯F–CH <sub>3</sub>                 | 0.2                | [27q]     |

[a] For computational details, see the original literature. Bz = benzyl.

The values in Table 1 are computed for dimers in optimal geometry undisturbed by their surroundings. In the solid state, hydrogen bonds are practically never in optimal geometry, and are always influenced by their environment. There are numerous effects from the close and also from the remote surrounding that may considerably increase or lower hydrogen bond energies (“crystal-field effects”). Hydrogen bonds do not normally occur as isolated entities but form networks. Within these networks, hydrogen bond energies are not additive (see Section 4). In such cases, it is not reasonable to split up the network into individual hydrogen bonds and to calculate energies for each one. In this sense, calculated hydrogen bond energies should always be taken with caution.

## 2.5. Transition to Other Interaction Types

As outlined previously, the hydrogen bond is composed of several constituent interactions which are variant in their contributing weights. Chemical variation of donor and/or acceptor, and possibly also of the environment, can gradually change a hydrogen bond to another interaction type. This shall be detailed here for the most important cases.

The transition to pure van der Waals interaction is very common. The polarity of X–H or A (or both) in the array X<sup>δ−</sup>–H<sup>δ+</sup>⋯A<sup>δ−</sup> can be reduced by suitable variation of X or A. This reduces the electrostatic part of the interaction, whereas the van der Waals component is much less affected. In consequence, the van der Waals component gains relative weight, and the angular characteristics gradually change from directional to isotropic. Since the polarities of X<sup>δ−</sup>–H<sup>δ+</sup> or A<sup>δ−</sup> can be reduced to zero continuously, the resulting transition of the interaction from hydrogen bond to van der Waals type is

continuous too. Such a behavior was actually demonstrated for the directionality of C–H⋯O=C interactions, which gradually disappears when the donor is varied from C≡C–H to C=CH<sub>2</sub> to C–CH<sub>3</sub> (see Figure 8, Section 3.2).<sup>[22]</sup> At the acceptor side of a hydrogen bond, sulfur is typical of an atom that allows continuous variation of the partial charge from S<sup>δ−</sup> to S<sup>δ+</sup>. Therefore, one can create a continuum of chemical situations between the S atom acting as a fairly strong hydrogen bond acceptor, and being inert to hydrogen bonding (the extreme cases are ionic species such as X–S<sup>−</sup> and X=S<sup>+</sup>–Y).

At the other end of the energy scale, there is a continuous transition to covalent bonding.<sup>[28]</sup> In the so-called symmetric hydrogen bonds X–H–X, where an H atom is equally shared between two chemically identical atoms X, no distinction can be made between a donor and an acceptor, or a “covalent” X–H and “noncovalent” H⋯X bond (found experimentally for X = F, O, and possibly N). In fact, this situation can be conveniently described as a hydrogen atom forming two covalent bonds with bond orders  $s = \frac{1}{2}$ . In crystals (and also in solution), all intermediate cases exist between the extremes X–H⋯⋯IX and X–H–X. Strongly covalent hydrogen bonds will be discussed in greater detail in Section 7, and the bond orders (“valences”) of H⋯O over the whole distance range will be given in Section 9 (Table 7).

There is also a gradual transition from hydrogen bonding to purely ionic interactions. If in an interaction X<sup>δ−</sup>–H<sup>δ+</sup>⋯Y<sup>δ−</sup>–H<sup>δ+</sup> the net charges on X–H and Y–H are zero, the electrostatics are of the dipole–dipole type. In general, however, the net charges are not zero. Alcoholic O–H groups have a partial negative charge in addition to their dipole moment, ammonium groups have a positive net charge, and so on. This situation leads to ionic interactions between the charge centers with the energy having a  $r^{-1}$  distance dependence. If the charges are large, the ionic behavior may become dominant. For fully charged hydrogen bond partners, energetics are typically dominated by the Coulombic interaction between the charge centers, but the total interaction still remains directional, with X–H not oriented at random but pointing at A. An important example are the so-called salt-bridges between primary ammonium and carboxylate groups in biological structures,<sup>[5]</sup> N<sup>+</sup>–H⋯O<sup>−</sup>. If weakly polar X–H groups are attached to a charged atom, such as the methyl groups in the N<sup>+</sup>Me<sub>4</sub> ion, they are often involved in short contacts to an approaching counterion, N<sup>+</sup>–X–H⋯A<sup>−</sup>.<sup>[8]</sup> Although these interactions are directional and may still be classified as a kind of hydrogen bond, their dominant part is certainly the ionic bond N<sup>+</sup>⋯A<sup>−</sup>.

Finally, there is a transition region between the hydrogen bond and the cation– $\pi$  interaction. In the pure cation– $\pi$  interaction a spherical cation such as K<sup>+</sup> contacts the negative charge concentration of a  $\pi$ -bonded moiety such as a phenyl ring. This can be considered an electrostatic monopole–quadrupole interaction. The bond energy is  $-19.2$  kcal mol<sup>-1</sup> for the example of K<sup>+</sup>⋯benzene.<sup>[29]</sup> A pure  $\pi$ -type hydrogen bond X<sup>δ−</sup>–H<sup>δ+</sup>⋯Ph is formally a dipole–quadrupole interaction with much lower energies of only a few kcal mol<sup>-1</sup> (Table 1). If charged hydrogen bond donors such as NH<sub>4</sub><sup>+</sup> interact with  $\pi$ -electron clouds, local dipoles are oriented at

the  $\pi$  face,<sup>[30]</sup> but the energetics are dominated by the charge–quadrupole interaction<sup>[27d]</sup> ( $\text{NH}_4^+ \cdots \text{Bz}$  experimentally:  $-19.3 \text{ kcal mol}^{-1}$ ).<sup>[29]</sup> If the X–H groups of the cation are only weakly polar, they may also orient at the  $\pi$  face and cause some modulation of the dominant cation– $\pi$  interaction, but this modulation fades to zero with decreasing X–H polarity.

## 2.6. Incipient Proton Transfer Reaction

A very important way of looking at hydrogen bonds is to regard them as incipient proton-transfer reactions. From this viewpoint, a stable hydrogen bond  $\text{X–H} \cdots \text{Y}$  is a “frozen” stage of the reaction  $\text{X–H} \cdots \text{Y} \rightleftharpoons \text{X}^- \cdots \text{H}^+ \cdots \text{Y}$  (or  $\text{X}^+ \cdots \text{H}^- \cdots \text{Y} \rightleftharpoons \text{X} \cdots \text{H}^+ \cdots \text{Y}$ , etc.). This means that a partial bond  $\text{H} \cdots \text{Y}$  is already established and the X–H bond is concomitantly weakened.<sup>[31]</sup> In the case of strong hydrogen bonds, the stage of proton transfer can be quite advanced. In some hydrogen bonds the proton position is not stable at X or Y, but proton transfer actually takes place with high rates. In other cases these rates are small or negligible.

The interpretation of hydrogen bonds as an incipient chemical reaction is complementary to electrostatic views on hydrogen bonding. It brings into play acid–base considerations, proton affinities, the partially covalent nature of the  $\text{H} \cdots \text{Y}$  bond, and turns out to be a very powerful concept for understanding the stronger types of hydrogen bonds in particular. For example, the partial  $\text{H} \cdots \text{Y}$  bond can only become strong if its orientation roughly coincides with the orientation of the full H–Y bond that would be formed upon proton transfer. Approach in different orientations may still be favorable in electrostatic terms, but results only in moderately strong hydrogen bonds.

This view also helps in deciding whether a particular type of  $\text{X–H} \cdots \text{A}$  interaction may be classified as a hydrogen bond or not (compare the definition in Section 2.1). *Only* if it may be thought of as a frozen proton-transfer reaction, may it be called a hydrogen bond.

## 2.7. Location of the H Atom

An atom is constituted of a nucleus and its electron shell. Normally, the centers of gravity of the nucleus and electron shell coincide well, and this common center is called the “location” of the atom. For H atoms, however, this is generally not the case. In a covalent bond with a more electronegative atom, the average position of the single electron of the H atom is displaced towards that other atom. The centers of gravity of the nucleus and electron no longer coincide, and this leads to a conceptual problem: what should be taken as the “location” of the atom? It is not chemically reasonable to consider one of the two centers of gravity as the “right” location of the atom, and the other as “wrong”, but one must accept that a point-atom model is simplistic in this situation.<sup>[32, 33]</sup> In practice, this leads to unpleasant complications. X-ray diffraction experiments determine electron-density distributions and locate the electron-density maxima of the atoms. Neutron diffraction, on the other hand, locates

the nuclei. The results of the two techniques for H atoms often differ by more than  $0.1 \text{ \AA}$ .<sup>[34]</sup> Neither of the two results is more true than the other, but they are complementary and both represent useful pieces of information. Nevertheless, neutron diffraction results are much more precise and reliable, and allow the proton positions to be located as accurately as other nuclei.

It has become a practice in the analysis of X-ray diffraction results to “normalize” the X–H bonds by shifting the position found for the H atom (that is, the position of the electron center of gravity) along the X–H vector to the average neutron-determined internuclear distance, namely, to the approximate position of the proton.<sup>[35]</sup> This theoretical position is then used for the calculation of hydrogen bond parameters. The currently used standard bond lengths are: O–H =  $0.983$ , N–H =  $1.009$ , C–H =  $1.083$ , B–H =  $1.19$ , and S–H =  $1.34 \text{ \AA}$ ; a more complete list can be found in ref. [8]. The normalization procedure is generally reasonable, well suited to smooth out the large experimental uncertainty of X-ray diffraction data, and is particularly useful in statistical database analysis. Nevertheless, one must be aware that it is not a correction in the strict sense, instead it replaces a certain structural feature (the location of the electron center of gravity) by a chemically different one (the proton position). Furthermore, the internuclear X–H bond length is fairly constant only in weak and moderate hydrogen bonds, whereas it is significantly elongated in strong ones. In the latter situation, the elongation should at least in principle be taken into account in the normalization. This requires, however, knowledge of the relationship between the relevant X–H and  $\text{H} \cdots \text{A}$  distances (see Section 3.6).<sup>[36]</sup>

## 2.8. Charge Density Properties

The precise mapping of the distribution of charge density in hydrogen-bonded systems is a classical topic in structural chemistry,<sup>[37]</sup> with a large number of individual studies reported.<sup>[38]</sup> Currently, Baders quantum theory of atoms in molecules (AIM) is the most frequently used formalism in theoretical analyses of charge density.<sup>[39]</sup> Each point in space is characterized by a charge density  $\rho(\mathbf{r})$ , and further quantities such as the gradient of  $\rho(\mathbf{r})$ , the Laplacian function of  $\rho(\mathbf{r})$ , and the matrix of the second derivatives of  $\rho(\mathbf{r})$  (Hessian matrix). The relevant definitions and the topology of  $\rho(\mathbf{r})$  in a molecule or molecular complex can be best understood with the help of an illustration (Figure 2; see figure legend for details).<sup>[40]</sup> The thin lines represent lines of steepest ascent through  $\rho(\mathbf{r})$  (trajectories). If there is a chemical bond between two atoms (such as a hydrogen bond), they are directly connected by a trajectory called the “bond path”. The point with the minimal  $\rho$  value along the bond path is called the “bond critical point” (BCP). It represents a saddle point of  $\rho(\mathbf{r})$  (strictly speaking, trajectories terminate at the BCP, so that the bond path represents a pair of trajectories each of which connects a nucleus with the BCP). Different kinds of chemical bonds have different numerical properties at the BCP, such as different electron density  $\rho_{\text{BCP}}$  and different

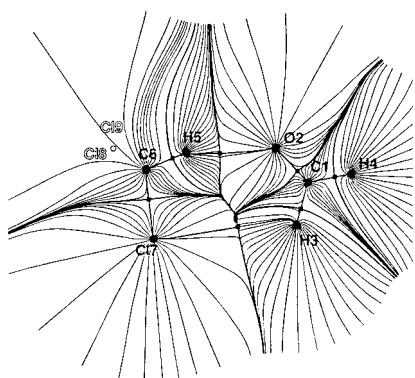


Figure 2. Representative topology of a theoretical electron density function in a hydrogen-bonded system: the adduct of chloroform and formaldehyde formed through a C–H $\cdots$ O hydrogen bond.<sup>[40]</sup> Thin lines represent lines of steepest ascent through  $\rho(r)$  (trajectories). Critical points (CP) of  $\rho(r)$  are maxima and points where the first derivative vanishes. There are four types of CPs in three-dimensional space (rank 3, that is, non-degenerate). Maxima are denoted (3, –3) and minima (3, +3). The latter are also called “cage critical points” (CCP). Saddle points representing a minimum in one direction of space and maxima in two perpendicular directions are called “bond critical points” (BCP) and denoted (3, –1). Saddle points, which represent minima in two perpendicular directions of space and a maximum in the third direction, are called “ring critical points” (RCP) and denoted (3, +1). The trajectories ending at a nucleus constitute a “molecular basin”. Basins of neighboring atoms are separated by trajectories that do not end at nuclei (namely, the “interatomic surface”). Trajectories connecting nuclei through a BCP are called a bond path. The electron density at BCPs are minima in the bond paths and maxima in the interatomic surface. BCPs are shown in the figure as squares.

values of the Laplacian function (negative for covalent bonds and H $\cdots$ A interactions of very strong hydrogen bonds, and positive for ionic bonds, van der Waals interactions, H $\cdots$ A interactions of medium strength, and weak hydrogen bonds).

The electron density at the bond critical point ( $\rho_{\text{BCP}}$ ) is higher in strong bonds than in weak ones. There are two bond critical points in a hydrogen bond X–H $\cdots$ A, one between X and H, and one between H and A. In normal hydrogen bonds, the  $\rho_{\text{BCP}}$  value in X–H is much larger than in H $\cdots$ A. The value of  $\rho_{\text{BCP}}$  in H $\cdots$ A increases with increasing hydrogen bond strength, while that in X–H decreases concomitantly. In the ideally centered case, X–H $\cdots$ X,  $\rho_{\text{BCP}}$  is equal for both bonds. This behavior has been nicely illustrated for O–H $\cdots$ O hydrogen bonds (Figure 3).<sup>[41]</sup> Bond paths with

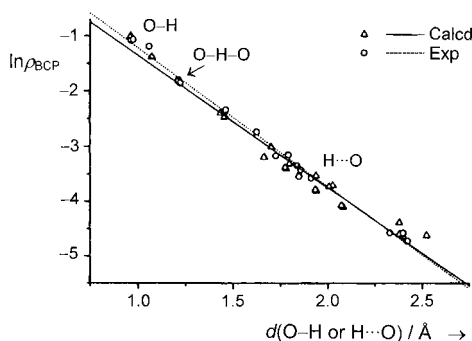


Figure 3. Electron density at the bond critical points,  $\rho_{\text{BCP}}$ , for a set of O–H $\cdots$ O hydrogen bonds, together with fitted logarithmic relationships for experimental and theoretical data. (Adapted from ref. [41].)

significant values of  $\rho_{\text{BCP}}$  have been calculated also for weaker hydrogen bonds of the types C–H $\cdots$ O<sup>[40]</sup> and C–H $\cdots$  $\pi$ <sup>[27]</sup>, as well as for “dihydrogen bonds”.<sup>[42]</sup> Electron-density properties of the agostic interaction relative to the hydrogen bond have also been characterized.<sup>[43]</sup>

Hydrogen bond properties are sometimes discussed exclusively in terms of topological analysis of theoretical  $\rho(r)$  distributions. Despite the merits of the method, it is unfortunate that discussion tends to be very formalistic, occasionally even overriding conflicts with experimental data.

## 2.9. IR and NMR Spectroscopic Properties

IR and NMR spectroscopy have both become standard methods to investigate hydrogen bonds in the solid state.<sup>[6]</sup> Nevertheless, they are not the focus of the present article and are, therefore, only briefly touched on here.

Formation of a hydrogen bond affects the vibrational modes of the groups involved in several ways.<sup>[44]</sup> For relatively simple systems, these effects can be studied quantitatively by solid-state IR spectroscopy. If there are many symmetry-independent bonded groups, however, band overlap normally prevents detailed analysis. The frequency of the donor X–H stretching vibration ( $\tilde{\nu}_{\text{X–H}}$ ) is best studied because it is (for polar X–H groups) quite easy to identify in absorption spectra, and in most cases very sensitive to the formation of hydrogen bonds (red-shift of the absorption band, band broadening or intensification). For O–H $\cdots$ O hydrogen bonds,  $\tilde{\nu}_{\text{O–H}}$  is correlated with the O $\cdots$ O distance (Figure 4).<sup>[45, 46]</sup> Analogous correlations have been established

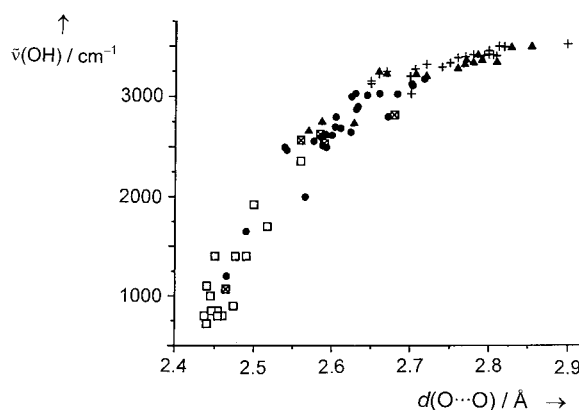


Figure 4. Scatter plot of IR stretching frequencies  $\tilde{\nu}_{\text{OH}}$  against O $\cdots$ O distances in O–H $\cdots$ O hydrogen bonds (squares: combination of acid and complementary base; filled circles: resonance-assisted hydrogen bonds (RAHB); triangles:  $\sigma$ -cooperative hydrogen bonds; crosses: isolated hydrogen bonds).<sup>[46]</sup> (IR data from ref. [45a].)

also for less common hydrogen bond types, for example, between the donor C $\equiv$ C–H and the acceptors O,<sup>[47]</sup> N,<sup>[48]</sup> and C=C.<sup>[49]</sup> There is considerable scatter in these correlations, not just because of experimental inaccuracy. The correlations represent systematic trends between different physical quantities, but not strict laws (for the discussion of an example, see footnote [50]).

The difference between the  $\tilde{\nu}_{\text{X-H}}$  value of free and hydrogen-bonded X-H groups,  $\Delta\tilde{\nu}_{\text{X-H}}$ , increases systematically with decreasing H...A (or X...A) distance. It has even been reported that a common correlation  $\Delta\tilde{\nu}_{\text{X-H}} = f(\text{H}\cdots\text{A})$  is approximately valid for many different types of X-H...A hydrogen bonds, and on the basis of a set of diverse organic and inorganic structures, it has been parametrized as  $\Delta\tilde{\nu}_{\text{X-H}} = 0.011 d_{\text{HA}}^{-6.1}$  ( $\tilde{\nu}_{\text{X-H}}$  in  $\text{cm}^{-1}$ ,  $d$  in nm).<sup>[51]</sup> An approximate relationship with bond enthalpies has also been established for O-H...O hydrogen bonds,  $-\Delta H = 0.134 d_{\text{HA}}^{-3.05}$  ( $H$  in  $\text{kJ mol}^{-1}$ ,  $d$  in nm; the equivalent relationship with band shifts is  $-\Delta H = 1.3 (\Delta\tilde{\nu})^{0.5}$ ).<sup>[51]</sup> The predictive power of these correlations is limited by the large scatter.

Further important properties of  $\nu_{\text{X-H}}$  are the band width and the integrated band intensity  $I(\tilde{\nu}_{\text{X-H}})$ . The band width and  $I(\tilde{\nu}_{\text{X-H}})$  increase strongly upon formation of a hydrogen bond, and this is often taken as a more reliable indicator of hydrogen bond formation than the red-shift of  $\nu_{\text{X-H}}$ . For example, there are cases of C-H...O hydrogen bonding where  $\Delta\nu_{\text{X-H}}$  is difficult to measure while the increase of  $I(\tilde{\nu}_{\text{X-H}})$  is easy to detect.<sup>[52]</sup> The increase of  $I(\tilde{\nu}_{\text{X-H}})$  has been correlated with the strength of the hydrogen bond, and the approximate relationship  $-\Delta H = 12.2 \Delta I(\tilde{\nu}_{\text{X-H}})^{0.5}$  was suggested.<sup>[53]</sup>

In principle, the H...A stretching vibration is the most direct spectroscopic indicator of hydrogen bonding. For weaker kinds of hydrogen bonds, these bands are in the far infrared, and are investigated only rarely. A direct effect of the hydrogen bond can often be observed also on the acceptor side. In X-H...O=C bonds, for example, the O=C bond is weakened leading to a lowering of the stretching vibration frequency.

The effects described above show many anomalies. For example, bond energies and dissociation constants of C-H...O interactions of chloroform molecules are substantial, but  $\nu_{\text{CH}}$  may not only shift to lower, but also to slightly higher wavenumbers. The band intensity always increases, as usual.<sup>[54]</sup> This effect, long regarded only as an exotic anomaly, has recently attracted greater attention. According to theoretical calculations,<sup>[55]</sup> a blue-shift of  $\nu_{\text{CH}}$  indicates a different kind of electronic interaction in the hydrogen bond: electron density of the acceptor is not mainly transferred into the antibonding  $\sigma^*$  orbital of the donor X-H, but into remote parts of the donor molecule (such as the C-Cl part of  $\text{CHCl}_3$ ). This transfer of electron density is also associated with a shortening of the X-H bond. The term "improper blue-shifting" hydrogen bonds was introduced to distinguish these interactions from "proper" hydrogen bonds.

In most hydrogen bonds several nuclei may be observed by NMR spectroscopy. In particular, the proton is increasingly deshielded with increasing hydrogen bond strength, which leads to  $^1\text{H}$  downfield shifts that are correlated with the length of the hydrogen bond.<sup>[6, 56]</sup> Thus, NMR shift data can be used to estimate lengths of hydrogen bonds (Figure 5). Chemical shifts of X and A (for example,  $^{15}\text{N}$ ), X/H and X/A coupling constants, and differences in the  $^1\text{H}$  and  $^2\text{H}$  signals in H/D exchange experiments can give additional information on X-H...A bonds. In O=C-OH...N(Py) hydrogen bonds, for example, the  $^{15}\text{N}$  chemical shift has been used to probe the protonation state of the N atom: in moderate strength

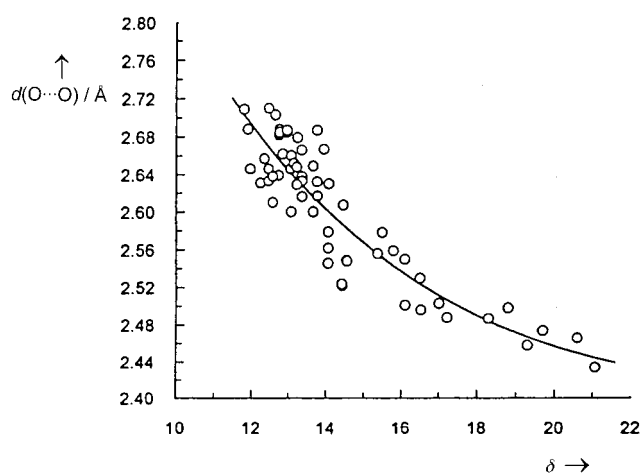


Figure 5. Typical correlation of  $^1\text{H}$  NMR chemical shift and O...O distance in O-H...O hydrogen bonds.<sup>[56c]</sup> Other authors have obtained similar figures from different structure samples.<sup>[6, 56a,b]</sup>

O-H...N hydrogen bonds the shift is  $< 20$ , in symmetric bonds O-H-N it is around  $\delta = -60$ , and in ionic bonds  $\text{O}^- \cdots \text{H-N}^+$  it becomes  $\delta = -100$ .<sup>[57]</sup> The time scale of proton dynamics in a disordered hydrogen bond can be determined from NMR experiments in a certain frame ( $\mu\text{s}$  scale) accessible to the experimental method.

## 2.10. The Categories of "Strong", "Moderate", and "Weak" Hydrogen Bonds

As we have seen, hydrogen bonds exist with a continuum of strengths. Nevertheless, it can be useful for practical reasons to introduce a classification, such as "weak", "strong", and possibly also "in between". In this article, the system described by Jeffrey is followed,<sup>[6]</sup> who called hydrogen bonds *moderate* if they resemble those between water molecules or in carbohydrates (one could also call them "normal"), and are associated with energies in the range 4–15  $\text{kcal mol}^{-1}$ . Hydrogen bonds with energies above and below this range are termed *strong* and *weak*, respectively. Some general properties of these categories are listed in Table 2. It must be stressed that there are no "natural" borderlines between these

Table 2. Strong, moderate, and weak hydrogen bonds following the classification of Jeffrey.<sup>[6]</sup> The numerical data are guiding values only.

|                                                                      | Strong                                      | Moderate                              | Weak                                    |
|----------------------------------------------------------------------|---------------------------------------------|---------------------------------------|-----------------------------------------|
| interaction type                                                     | strongly covalent                           | mostly electrostatic                  | electrostat./dispers.                   |
| bond lengths [ $\text{\AA}$ ]                                        |                                             |                                       |                                         |
| H...A                                                                | 1.2–1.5                                     | 1.5–2.2                               | $> 2.2$                                 |
| lengthening of X-H [ $\text{\AA}$ ]                                  | 0.08–0.25                                   | 0.02–0.08                             | $< 0.02$                                |
| X-H versus H...A                                                     | $\text{X-H} \approx \text{H}\cdots\text{A}$ | $\text{X-H} < \text{H}\cdots\text{A}$ | $\text{X-H} \ll \text{H}\cdots\text{A}$ |
| X...A [ $\text{\AA}$ ]                                               | 2.2–2.5                                     | 2.5–3.2                               | $> 3.2$                                 |
| directionality                                                       | strong                                      | moderate                              | weak                                    |
| bond angles [ $^\circ$ ]                                             | 170–180                                     | $> 130$                               | $> 90$                                  |
| bond energy [ $\text{kcal mol}^{-1}$ ]                               | 15–40                                       | 4–15                                  | $< 4$                                   |
| relat. IR shift $\Delta\tilde{\nu}_{\text{XH}}$ [ $\text{cm}^{-1}$ ] | 25%                                         | 10–25%                                | $< 10\%$                                |
| $^1\text{H}$ downfield shift                                         | 14–22                                       | $< 14$                                |                                         |

categories, and that there is no point in using this or any related system in too stringent a way. For a comment on the names of the categories, see footnote [58].

### 3. Geometry

Hydrogen bonds and their environment have a well-defined geometry in the crystalline state. More than 200 000 published organic and organometallic crystal structures provide a vast amount of experimental data that allows hydrogen bond geometries to be analyzed at a high statistical level.<sup>[10]</sup> The results of such analyses are presented in this section.

#### 3.1. Donor Directionality

The main structural feature distinguishing the hydrogen bond from the van der Waals interaction is preference for linearity. As a typical example, the distribution of angles  $\theta$  in carbohydrates is shown in Figure 6 ( $\text{H}\cdots\text{O} < 2.0 \text{ \AA}$ ). The absolute frequencies peak between 160 and 170° (Figure 6a); these are the angles that occur most frequently in crystals. To obtain the more relevant frequencies per solid angle, one must weight the absolute values with  $1/\sin\theta$  ("cone correction").<sup>[59]</sup> The weighted frequencies clearly peak at linear angles (Figure 6b).

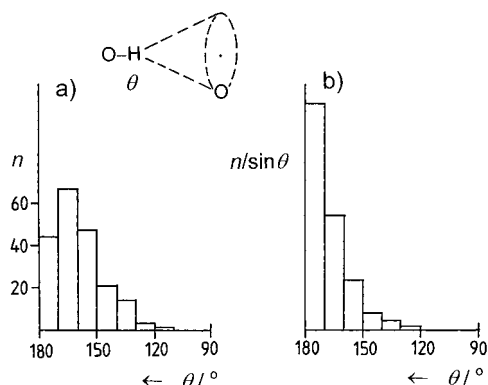


Figure 6. Directionality of  $\text{O}-\text{H}\cdots\text{O}$  hydrogen bonds in carbohydrates ( $\text{H}\cdots\text{O} < 2.0 \text{ \AA}$ ). a) Conventional histogram with a maximum at slightly bent angles  $\theta$ . b) Histogram after "cone correction" (weighting with  $1/\sin\theta$ ) which represents the frequency of H-bonds per solid angle.<sup>[59]</sup> Angular preferences can be seen properly only after cone correction.

The histograms in Figure 6 do not contain distance information, and this is a significant disadvantage. A better (but more costly) way to analyze angular preferences is in scatter plots of angles  $\theta$  against distances  $d$ . This is illustrated for the example of  $\text{X}-\text{H}\cdots\text{Cl}^-$  interactions in Figure 7 (for hydroxy donors in Figure 7a and for  $\text{NH}_3^+$  donors in Figure 7b).<sup>[60]</sup> The plots include all contacts found in crystal structures with  $d < 4.0 \text{ \AA}$  at any occurring angle. There are densely populated clusters of data points at short distances and fairly linear angles, and each point in these clusters represents a hydrogen bond. The scatter within the clusters is considerable, and their borders are diffuse. The shortest distances occur at relatively

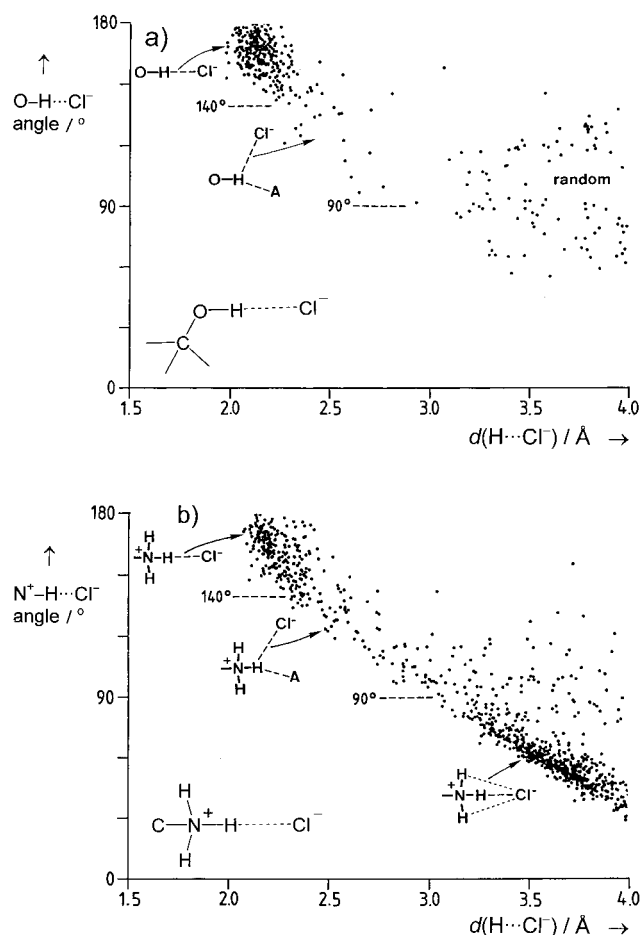


Figure 7. Angular scatter plot of  $\text{X}-\text{H}\cdots\text{Cl}^-$  angles against  $\text{H}\cdots\text{Cl}^-$  distances for a) hydroxy and b)  $-\text{NH}_3^+$  donors ( $\text{X}-\text{H}$  bonds normalized).<sup>[60]</sup> All contacts with  $\text{H}\cdots\text{Cl}^- < 4.0 \text{ \AA}$  are included, whether they represent a hydrogen bond or not.

linear angles  $\theta$ , whereas longer bonds are observed with a larger angular range. At longer distances and bent angles, a weakly populated region represents minor components of bifurcated hydrogen bonds (Scheme 2). The regions to the right of these clusters are almost empty, which shows that very long but linear hydrogen bonds almost do not occur (compare with Figure 1). At long distances there is a region of random scatter, which corresponds to  $\text{X}-\text{H}$  groups and chloride ions that do not form a direct interaction. The plots are unpopulated at short distances, because exchange repulsion prevents shorter approach.

The detailed appearance of the plots depends on the type of donor. With the hydroxy group as a donor (Figure 7a), the picture contains only the arrays mentioned above, and the hydrogen bond region is fairly well separated from the region of random scatter. With the more complicated donor  $-\text{NH}_3^+$  (Figure 7b), there is an additional, densely populated feature at long distances and very bent angles  $\theta < 90^\circ$ . This new cluster represents the two H atoms of  $-\text{NH}_3^+$  that point away from the chloride ion if a  $-\text{NH}_3^+\cdots\text{Cl}^-$  hydrogen bond is formed. There is a much higher density of bifurcated hydrogen bonds in Figure 7b than in Figure 7a, and all the populated regions merge into each other. Plots analogous to Figure 7 have been published for other special kinds of

hydrogen bonds, such as  $\text{O}-\text{H}\cdots\text{O}$ <sup>[61]</sup> and  $\text{C}-\text{H}\cdots\text{O}$  interactions in carbohydrates,<sup>[62]</sup> and with more-limited angular ranges for general  $\text{O}-\text{H}\cdots\text{O}$  and  $\text{N}-\text{H}\cdots\text{O}$ ,<sup>[63]</sup> water–water,<sup>[64]</sup>  $\text{N}/\text{O}-\text{H}\cdots\text{Ph}$ ,<sup>[65]</sup>  $\text{C}-\text{H}\cdots\text{Cl}(\text{C})$ ,<sup>[66]</sup> and even  $\text{C}-\text{H}\cdots\text{F}(\text{C})$ <sup>[67]</sup> hydrogen bonds. These figures all show the same general features (preference of linearity) with some variation in the details, which indicates that the angular characteristics of all kinds of hydrogen bonds are related.

The degree of directionality depends on the polarity of the donor. This effect is shown in Figure 8 with cone-corrected angular histograms of normal hydrogen bonds  $\text{O}-\text{H}\cdots\text{O}=\text{C}$ , of  $\text{C}-\text{H}\cdots\text{O}=\text{C}$  interactions with three  $\text{C}-\text{H}$  types of different polarities, and, for comparison, also of  $\text{C}-\text{H}\cdots\text{H}-\text{C}$  van der Waals contacts.<sup>[22]</sup> The degree of directionality decreases in parallel with the polarity of the  $\text{X}-\text{H}$  group, namely,  $\text{O}-\text{H} > \text{C}\equiv\text{C}-\text{H} > \text{C}=\text{CH}_2 > -\text{CH}_3$ . Note that  $\text{C}-\text{H}\cdots\text{O}$  contacts of methyl groups still show a weak but significant preference for linearity that is clearly different from van der Waals contacts. This is experimental evidence that methyl  $\text{C}-\text{H}\cdots\text{O}$  interactions deserve to be classified as hydrogen bonds (very weak ones, though).

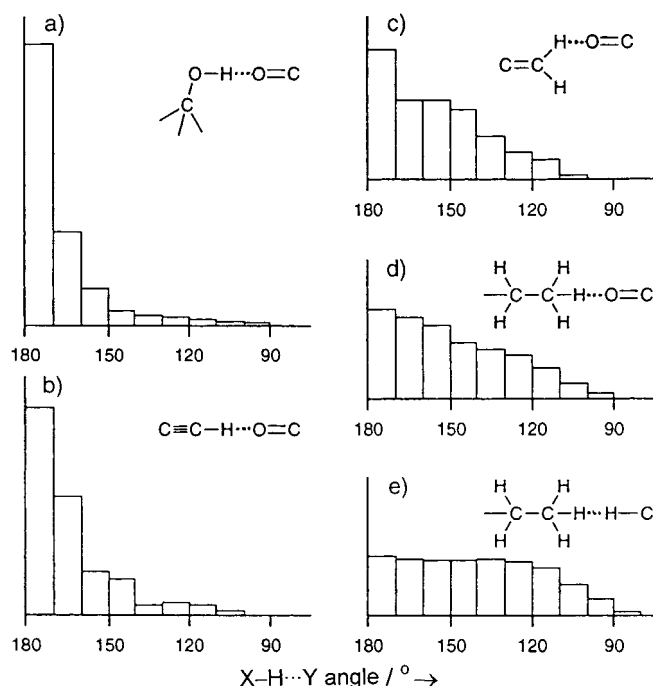


Figure 8. Directionality of  $\text{X}-\text{H}\cdots\text{O}=\text{C}$  interactions with  $\text{X}-\text{H}$  groups of different polarities (cone-corrected angular histograms). a) Hydroxy, b)  $\text{C}\equiv\text{C}-\text{H}$ , c)  $\text{C}=\text{CH}_2$ , d)  $-\text{CH}_3$  donors, e)  $\text{C}-\text{H}\cdots\text{H}-\text{C}$  van der Waals contacts. The degree of directionality decreases gradually from (a) to (d), and interaction (e) is isotropic within a broad angular range. Note that the picture for  $\text{C}\equiv\text{C}-\text{H}$  is similar to that for the conventional  $\text{O}-\text{H}$  donor.  $\text{C}-\text{H}\cdots\text{O}=\text{C}$  interactions of methyl groups are still directional, but to a much smaller extent than  $\text{C}\equiv\text{C}-\text{H}\cdots\text{O}=\text{C}$  hydrogen bonds.<sup>[22]</sup>

### 3.2. Acceptor Directionality

Hydrogen bonds are directional also at the acceptor side. For strong hydrogen bonds (but only for these essentially), the directionality of the acceptor corresponds to the geometry of the covalent product obtained in a hypothetical proton-

transfer reaction. The directionality of moderate and weak hydrogen bonds is much softer, but can still be identified with the orientation of electron lone pairs (in rare cases<sup>[68]</sup> also with filled  $d_{z^2}$  orbitals of transition metal atoms). In the classical example of carbonyl groups, the oxygen lone pair lobes are in the  $\text{R}_2\text{C}=\text{O}$  plane and form angles of about  $120^\circ$  with the  $\text{C}=\text{O}$  bond. As is seen in an angular histogram with  $\text{N}/\text{O}-\text{H}$  donors (Figure 9, bottom), a corresponding acceptor directionality is indeed present, but it is softer than is often assumed.<sup>[69]</sup> A similar distribution has also been found with stronger types of  $\text{C}-\text{H}$  donors ( $\text{C}\equiv\text{CH}$ ,  $\text{Cl}_3\text{CH}$ ,  $\text{Cl}_2\text{CH}_2$ ).<sup>[70]</sup> It is interesting that the acceptor directionality is much more pronounced for thiocarbonyl groups, with lone pair directions forming an angle of only  $105^\circ$  with  $\text{C}=\text{S}$  (Figure 9, top).<sup>[69]</sup> The  $\text{C}=\text{Se}\cdots\text{H}$  angle in selenocarbonyl acceptors is even closer to rectangular.<sup>[8]</sup>

For hydroxy and water acceptors, the electronic structure would predict a bimodal distribution with two preferred directions in roughly tetrahedral geometry with respect to the

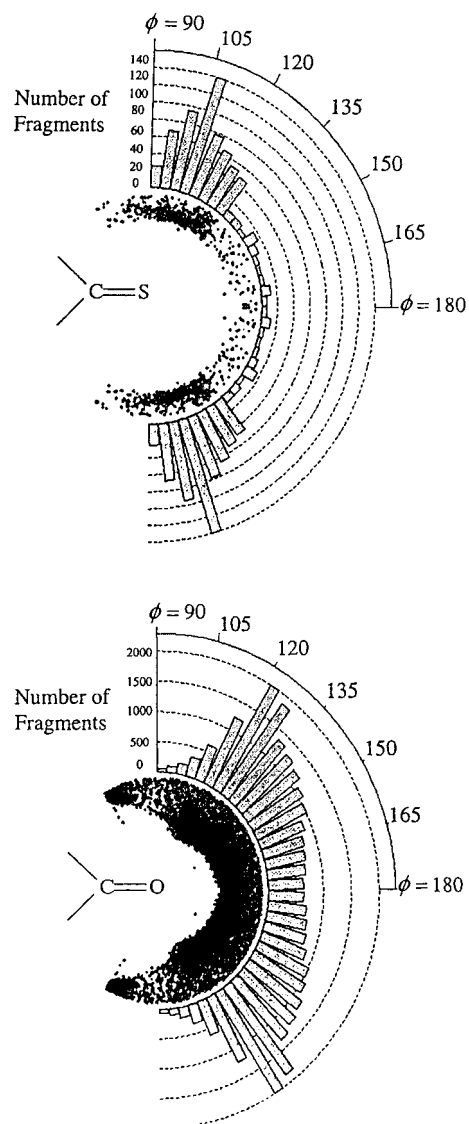
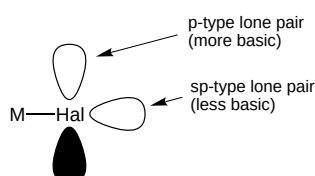


Figure 9. Acceptor directionality of  $\text{C}=\text{O}$  (bottom) and  $\text{C}=\text{S}$  (top) groups in  $\text{N}/\text{O}-\text{H}\cdots\text{O}/\text{S}=\text{C}$  hydrogen bonds.<sup>[69]</sup> Note that the directionality is much more blurred for  $\text{C}=\text{O}$  than for  $\text{C}=\text{S}$ .

two covalent bonds at the O atom. The actual directionality, however, is so soft that clustering is only observed in the bisecting plane of  $R^1-O-R^2$ , without separation into two modes.<sup>[71]</sup> The acceptor directionality of the pyridyl N atom has also been characterized in a statistical study.<sup>[72]</sup>

Of more recent interest are hydrogen bonds with halogen acceptors. A metal-bonded halogen atom is strongly polar and a good acceptor. The electronic structure suggests different basicity characteristics of the different electron lone pairs (Scheme 3),<sup>[73]</sup> and indeed,  $X-H \cdots Cl-M$  hydrogen bonds in crystals are almost exclusively donated roughly perpendicular to the  $M-Cl$  bond (angular range  $80-140^\circ$ ).<sup>[73, 74]</sup> An exception among the metal-bonded halogens is fluorine, which shows a much more isotropic behavior.<sup>[75]</sup>



Scheme 3. The electron lone pairs of metal-bonded halogen.<sup>[73]</sup>

Most complex, and not yet fully explored, is the directionality of  $\pi$  acceptors. For the simplest one,  $C \equiv C$ , it seems that hydrogen bonds are preferably directed at the midpoint of the triple bond, but may point also at individual C atoms.<sup>[8]</sup> For the most important  $\pi$  acceptor, the Ph group, the potential energy surface of  $X-H \cdots Ph$  interactions is very flat, which allows large movements of the donor over the  $\pi$  face without much of a difference in energy.<sup>[27i,k, 76]</sup> Consensus has not been reached concerning the location of the global energy minimum: does it occur with the  $X-H$  vector exactly over the ring midpoint (then,  $X-H$  can interact with *all* electrons of the  $\pi$  system), or does  $X-H$  point at an individual C-C bond or even a C atom? All these geometries, and also all intermediate situations, are found in crystals. Two extreme cases are illustrated in Figure 10 (for details, see legend).<sup>[77, 78]</sup> The large size of the  $\pi$  face makes the Ph acceptor a “target that is easy to hit”.<sup>[79]</sup> This has important consequences for the role of the phenyl group in the packing of organic molecules,<sup>[8]</sup> and also for its role as a reserve acceptor in biological substances.<sup>[80]</sup> In the case of a local deficiency of conventional acceptors, a donor can form an  $X-H \cdots Ph$  hydrogen bond instead if a Ph group is available even only in a roughly suitable geometry.

### 3.3. Distributions and Mean Values of the $H \cdots A$ Bond Lengths

Hydrogen bond lengths  $d$  in the solid state are very variable. Distances and angles vary in wide ranges even with a constant donor–acceptor combination, as shown already for the example  $C-OH \cdots Cl^-$  in the  $d-\theta$  scatter plot shown in Figure 7a. Here, the broad scatter can not be a consequence of chemical variations, but only of crystal packing forces that affect each hydrogen bond in a different way (for a more detailed discussion of this matter, see Section 5).

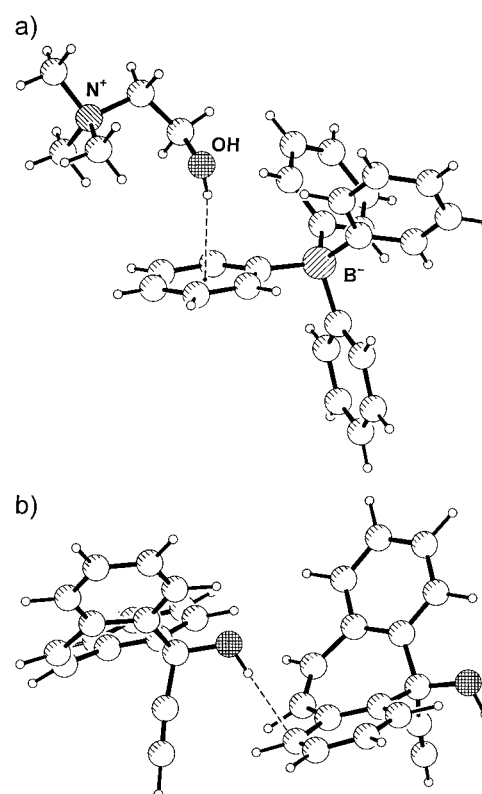


Figure 10.  $O-H \cdots Ph$  hydrogen bonds with different geometries. a) The donor is positioned almost exactly over the aromatic midpoint  $M$ ; the six  $H \cdots C$  distances are in the range  $2.49-2.70$  Å;  $H \cdots M$  is much shorter,  $2.17$  Å, and the  $O-H \cdots M$  angle is  $160^\circ$  (X-ray crystal structure of choline tetraphenylborate).<sup>[77]</sup> b) The donor is oriented directly at a C atom,  $H \cdots C = 2.34$  Å, angle  $O-H \cdots C = 174^\circ$  (neutron diffraction crystal structure of 5-ethynyl-5H-dibenzo[*a,d*]cyclohepten-5-ol).<sup>[78]</sup>

If one wants to display bond lengths in a histogram, a cutoff in the angle  $\theta$  has to be selected. If only linear hydrogen bonds are of interest, one may select  $\theta > 135^\circ$  and arrive at a distribution such as the one shown in Figure 11a for  $-N^+H_3 \cdots Cl^-$  hydrogen bonds. There is a distinct maximum, and the distribution has a well-defined beginning and a fairly

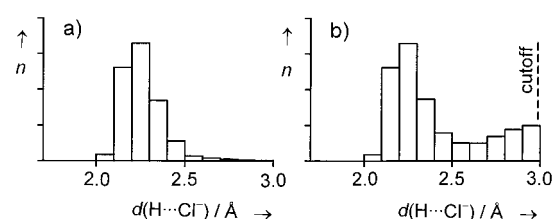


Figure 11. Typical  $H \cdots A$  bond-length distributions:  $-NH_3^+ \cdots Cl^-$  hydrogen bonds up to a cutoff of  $d = 3.0$  Å (data as for in Figure 7b). a) Only fairly linear hydrogen bonds with  $\theta > 135^\circ$ . This histogram contains data from a horizontal slice  $180 > \theta > 135^\circ$  of Figure 7b. b) With the generous angle cutoff  $\theta > 90^\circ$ . This histogram contains data from the slice  $180 > \theta > 90^\circ$  of Figure 7b.

well defined end with only a few outliers. For weak hydrogen bond types (or severely sterically hindered ones), the distribution does not fall to zero at long distances but fades into the continuum of random contacts.<sup>[81]</sup> If a more generous

angle cutoff is chosen, such as  $\theta > 110^\circ$  or  $90^\circ$ , the distance distribution will typically look like the one in Figure 11 b. Minor components of multifurcated interactions are now included, and as a consequence, the distribution no longer goes to zero at longer distances: following a certain minimum, the frequency of contacts increases again and merges with the continuum of random contacts. Since the relative content of multifurcated bonds is strongly sample-dependent (see Section 3.4), the exact shape of the long-distance region of such histograms is strongly sample-dependent too. Statistical

characterization of such distributions (such as Figure 11 b) is difficult.<sup>[82]</sup>

Figures 7 and 11 show the geometry variation for a constant donor–acceptor combination. If the donor and/or acceptor are chemically varied, new pictures are obtained which differ in the mean distance and the degree of directionality. Relatively comprehensive (and new) numerical data are compiled in Tables 3 and 4 for hydrogen bonds involving water molecules to shed light on the general rules determining mean hydrogen bond lengths.<sup>[10]</sup>

Table 3. Hydrogen bonds with water molecules as acceptors ( $X-H \cdots O_W$ ): Geometry of fairly linear interactions ( $\theta > 135^\circ$ ) with various donors (distances are given in Å). (Database information was retrieved for this article.<sup>[10a]</sup>)

| Donor                     | <i>n</i> | Mean $H \cdots O_W$ distance | Mean $X \cdots O_W$ distance | $H \cdots O_W$ distance (95 %) <sup>[a]</sup> | $X \cdots O_W$ distance (95 %) <sup>[a]</sup> |
|---------------------------|----------|------------------------------|------------------------------|-----------------------------------------------|-----------------------------------------------|
| <i>O–H donors</i>         |          |                              |                              |                                               |                                               |
| $H_3O^+$                  | 21       | 1.54(2)                      | 2.49(2)                      | –                                             | –                                             |
| $N^+-OH$                  | 1        | 1.57(–)                      | 2.55(–)                      | –                                             | –                                             |
| $S-OH$                    | 4        | 1.58(–)                      | 2.55(–)                      | –                                             | –                                             |
| $P-OH$                    | 73       | 1.61(1)                      | 2.575(9)                     | 1.44–1.77                                     | 2.42–2.72                                     |
| $Se-OH$                   | 4        | 1.62(–)                      | 2.59(–)                      | –                                             | –                                             |
| $O=C-OH$                  | 244      | 1.629(4)                     | 2.591(4)                     | 1.51–1.78                                     | 2.49–2.75                                     |
| $N=C-OH$                  | 6        | 1.69(3)                      | 2.60(3)                      | –                                             | –                                             |
| $N-OH$                    | 46       | 1.68(1)                      | 2.65(1)                      | –                                             | –                                             |
| $C=C-OH$ , $Ph-OH$        | 162      | 1.724(8)                     | 2.679(7)                     | 1.55–1.96                                     | 2.52–2.88                                     |
| $As-OH$                   | 4        | 1.75(–)                      | 2.68(–)                      | –                                             | –                                             |
| $O-OH$                    | 2        | 1.76(–)                      | 2.69(–)                      | –                                             | –                                             |
| $C_{sp^3}-OH$             | 763      | 1.804(4)                     | 2.753(3)                     | 1.64–2.06                                     | 2.61–2.97                                     |
| $3(TM)OH^{[b]}$           | 6        | 1.81(5)                      | 2.76(4)                      | –                                             | –                                             |
| $2(TM)OH^{[b]}$           | 14       | 1.85(4)                      | 2.79(4)                      | –                                             | –                                             |
| $H_2O$                    | 2505     | 1.880(2)                     | 2.825(2)                     | 1.72–2.19                                     | 2.68–3.11                                     |
| $B^+-OH$                  | 5        | 1.91(–)                      | 2.86(–)                      | –                                             | –                                             |
| $TM-OH^{[b]}$             | 5        | 1.96(–)                      | 2.89(–)                      | –                                             | –                                             |
| $^+OH$                    | 2        | 2.27(–)                      | 3.22(–)                      | –                                             | –                                             |
| <i>N–H donors</i>         |          |                              |                              |                                               |                                               |
| $(SO_2, SO_2)NH$          | 7        | 1.71(1)                      | 2.70(1)                      | –                                             | –                                             |
| $Im^+N-H$                 | 20       | 1.74(2)                      | 2.73(2)                      | –                                             | –                                             |
| $Py^+N-H$                 | 67       | 1.78(1)                      | 2.75(1)                      | 1.63–2.05                                     | 2.63–2.96                                     |
| $(C,C,C)N^+-H$            | 40       | 1.82(2)                      | 2.77(1)                      | –                                             | –                                             |
| $(C,C)N^+H_2$             | 108      | 1.87(1)                      | 2.83(1)                      | 1.68–2.19                                     | 2.68–3.06                                     |
| $(C_{sp^2}, C_{sp^2})N-H$ | 316      | 1.860(8)                     | 2.835(7)                     | 1.69–2.20                                     | 2.69–3.13                                     |
| $C-NH_3^+$                | 370      | 1.878(6)                     | 2.840(5)                     | 1.71–2.17                                     | 2.71–3.08                                     |
| $NH_4^+$                  | 86       | 1.95(1)                      | 2.91(1)                      | 1.74–2.24                                     | 2.73–3.11                                     |
| $(C_{sp^2}, C_{sp^3})N-H$ | 178      | 1.988(9)                     | 2.937(8)                     | 1.79–2.25                                     | 2.77–3.18                                     |
| (peptide) $N-H$           | 118      | 1.99(1)                      | 2.94(1)                      | 1.80–2.31                                     | 2.77–3.18                                     |
| $C_{sp^2}-NH_2$           | 508      | 2.016(6)                     | 2.963(5)                     | 1.81–2.31                                     | 2.78–3.21                                     |
| $(TM, C, C)N-H^{[b]}$     | 128      | 2.05(1)                      | 2.99(1)                      | 1.82–2.35                                     | 2.82–3.24                                     |
| $(TM, C_{sp^2})N-H^{[b]}$ | 18       | 2.07(3)                      | 3.03(3)                      | –                                             | –                                             |
| $(TM, C)NH_2^{[b]}$       | 467      | 2.084(6)                     | 3.031(5)                     | 1.88–2.35                                     | 2.86–3.27                                     |
| $TM-NH_3^{[b]}$           | 68       | 2.09(2)                      | 3.03(1)                      | 1.90–2.35                                     | 2.89–3.28                                     |
| $(C_{sp^3}, C_{sp^3})N-H$ | 13       | 2.14(3)                      | 3.08(2)                      | –                                             | –                                             |
| $C_{sp^3}-NH_2$           | 20       | 2.12(4)                      | 3.09(4)                      | –                                             | –                                             |
| $N-NH_2$                  | 5        | 2.16(–)                      | 3.09(–)                      | –                                             | –                                             |
| <i>S–H donors</i>         |          |                              |                              |                                               |                                               |
| $C-SH$                    | 1        | 2.16(–)                      | 3.48(–)                      | –                                             | –                                             |
| <i>C–H donors</i>         |          |                              |                              |                                               |                                               |
| $Cl_3C-H$                 | 2        | 2.06(–)                      | 3.07(–)                      | –                                             | –                                             |
| $C\equiv C-H$             | 3        | 2.10(–)                      | 3.16(–)                      | –                                             | –                                             |
| $Cl_2CH_2$                | 2        | 2.16(–)                      | 3.22(–)                      | –                                             | –                                             |
| $(N,N)C_{sp^2}-H$         | 32       | 2.41(3)                      | 3.38(3)                      | –                                             | –                                             |
| $(Cl,C)C_{sp^3}-H$        | 6        | 2.46(9)                      | 3.44(5)                      | –                                             | –                                             |
| $(N,C)C_{sp^2}-H$         | 276      | 2.48(1)                      | 3.47(1)                      | > 2.12                                        | > 3.14                                        |
| $(C,C)C_{sp^2}-H$         | 1369     | 2.553(4)                     | 3.540(4)                     | > 2.22                                        | > 3.23                                        |
| $(C,C,C)C_{sp^3}-H$       | 29       | 2.59(2)                      | 3.59(2)                      | –                                             | –                                             |
| $O-CH_3$                  | 80       | 2.59(2)                      | 3.59(2)                      | > 2.32                                        | > 3.32                                        |
| $C_{sp^3}-CH_3$           | 533      | 2.632(6)                     | 3.613(6)                     | > 2.37                                        | > 3.35                                        |

[a] The “95 % ranges” of  $H \cdots O_W$  and  $X \cdots O_W$  distances include 95 % of the hydrogen bonds. They are given only if  $n > 50$ . For distributions without a pronounced maximum, the 2.5th percentile is given instead of the central 95 %. [b] TM = transition metal atom.



Table 4.  $O_W-H\cdots A$  hydrogen bonds from water donor molecules that are not coordinated to transition metal atoms. Geometry of fairly linear interactions ( $\theta > 135^\circ$ ) for various acceptors (distances in Å). (Database information was retrieved for this article.<sup>[10b]</sup>)

| Acceptor                          | <i>n</i> | Mean $H\cdots A$ distance | Mean $O_W\cdots A$ distance | $H\cdots A$ distance (95 %) <sup>[a]</sup> | $O_W\cdots A$ distance (95 %) <sup>[a]</sup> |
|-----------------------------------|----------|---------------------------|-----------------------------|--------------------------------------------|----------------------------------------------|
| <i>O acceptors</i>                |          |                           |                             |                                            |                                              |
| $^-OH$                            | 8        | 1.71(3)                   | 2.69(3)                     | –                                          | –                                            |
| $Se=O$                            | 6        | 1.79(2)                   | 2.74(2)                     | –                                          | –                                            |
| $As=O$                            | 11       | 1.84(3)                   | 2.76(2)                     | –                                          | –                                            |
| $P=O, P-O^-$                      | 664      | 1.846(4)                  | 2.793(4)                    | 1.69–2.09                                  | 2.65–3.01                                    |
| $N^+-O^-$                         | 50       | 1.84(2)                   | 2.80(1)                     | 1.66–2.12                                  | 2.64–3.03                                    |
| $(C,C)C-O^-$                      | 95       | 1.85(1)                   | 2.80(1)                     | 1.62–2.17                                  | 2.59–3.11                                    |
| $-COO^-$                          | 1035     | 1.859(4)                  | 2.807(3)                    | 1.72–2.07                                  | 2.69–2.99                                    |
| $H_2O$                            | 2505     | 1.880(2)                  | 2.825(2)                    | 1.72–2.19                                  | 2.68–3.11                                    |
| $R_2C=O$                          | 2485     | 1.900(3)                  | 2.840(2)                    | 1.73–2.23                                  | 2.69–3.11                                    |
| $C_{sp^3}-OH$                     | 757      | 1.891(4)                  | 2.831(4)                    | 1.73–2.19                                  | 2.69–3.07                                    |
| $TM-O-C^{[b]}$                    | 560      | 1.902(6)                  | 2.842(6)                    | 1.66–2.24                                  | 2.63–3.12                                    |
| $S=O, S-O^-$                      | 668      | 1.914(5)                  | 2.854(4)                    | 1.74–2.27                                  | 2.70–3.15                                    |
| $B^-O-C$                          | 23       | 1.92(3)                   | 2.86(2)                     | –                                          | –                                            |
| $TM=O, TM-O^{[b]}$                | 218      | 1.94(1)                   | 2.877(8)                    | 1.73–2.30                                  | 2.70–3.16                                    |
| $TM-O_2^{[b]}$                    | 16       | 1.95(3)                   | 2.88(2)                     | –                                          | –                                            |
| $Ph-OH$                           | 89       | 1.97(1)                   | 2.89(1)                     | 1.72–2.27                                  | 2.62–3.17                                    |
| $C-O-C$                           | 254      | 1.978(9)                  | 2.910(7)                    | 1.78–2.33                                  | 2.74–3.17                                    |
| $N-OH$                            | 20       | 1.99(3)                   | 2.91(2)                     | –                                          | –                                            |
| $P-OH$                            | 34       | 1.97(2)                   | 2.91(2)                     | –                                          | –                                            |
| $NO_3^-$                          | 195      | 2.00(1)                   | 2.927(9)                    | 1.77–2.36                                  | 2.69–3.24                                    |
| $(O=C)-OH$                        | 35       | 2.01(3)                   | 2.94(3)                     | –                                          | –                                            |
| $Sb-O-C$                          | 20       | 2.03(4)                   | 2.95(3)                     | –                                          | –                                            |
| $ClO_4^-$                         | 180      | 2.07(1)                   | 2.98(1)                     | 1.80–2.36                                  | 2.73–3.25                                    |
| $Te-OH$                           | 5        | 2.07(–)                   | 2.99(–)                     | –                                          | –                                            |
| $C-NO_2$                          | 57       | 2.13(2)                   | 3.04(2)                     | 1.85–2.38                                  | 2.80–3.17                                    |
| $TM-CO^{[b]}$                     | 4        | 2.30(–)                   | 3.11(–)                     | –                                          | –                                            |
| <i>N acceptors</i>                |          |                           |                             |                                            |                                              |
| $C_{sp^3}-NH_2$                   | 17       | 1.88(2)                   | 2.84(1)                     | –                                          | –                                            |
| $C_{sp^3}, C_{sp^3}NH$            | 23       | 1.93(3)                   | 2.89(2)                     | –                                          | –                                            |
| $N=N-N$                           | 13       | 1.94(2)                   | 2.89(2)                     | –                                          | –                                            |
| $C_{sp^3}, C_{sp^3}, C_{sp^3}N$   | 78       | 1.96(1)                   | 2.90(1)                     | 1.78–2.27                                  | 2.76–3.20                                    |
| $C=N-C$                           | 345      | 1.959(6)                  | 2.905(6)                    | 1.79–2.26                                  | 2.75–3.17                                    |
| $C=N-O$                           | 24       | 1.99(3)                   | 2.94(2)                     | –                                          | –                                            |
| $-C\equiv N$                      | 43       | 2.00(2)                   | 2.94(2)                     | –                                          | –                                            |
| $C_{sp^3}-NH_2$                   | 25       | 2.03(3)                   | 2.95(2)                     | –                                          | –                                            |
| $C\sim N\sim N$                   | 50       | 2.03(2)                   | 2.96(2)                     | –                                          | –                                            |
| $C=N-S$                           | 9        | 2.09(6)                   | 3.03(5)                     | –                                          | –                                            |
| <i>S acceptors</i>                |          |                           |                             |                                            |                                              |
| $C-S^-$                           | 68       | 2.38(1)                   | 3.31(1)                     | 2.22–2.61                                  | 3.19–3.51                                    |
| $P=S, P-S^-$                      | 12       | 2.35(2)                   | 3.31(1)                     | –                                          | –                                            |
| $Sn-S^-$                          | 7        | 2.41(2)                   | 3.33(3)                     | –                                          | –                                            |
| $R_2C=S$                          | 73       | 2.42(1)                   | 3.36(1)                     | 2.26–2.65                                  | 3.24–3.58                                    |
| $TM-S-C^{[b]}$                    | 16       | 2.51(3)                   | 3.43(3)                     | –                                          | –                                            |
| $C-S-C$                           | 2        | 2.60(–)                   | 3.53(–)                     | –                                          | –                                            |
| <i>Se acceptors</i>               |          |                           |                             |                                            |                                              |
| $Se$                              | 3        | 2.45(–)                   | 3.40(–)                     | –                                          | –                                            |
| <i>Halogen acceptors</i>          |          |                           |                             |                                            |                                              |
| $F^-$                             | 13       | 1.70(2)                   | 2.67(2)                     | –                                          | –                                            |
| $SiF_6^{2-}$                      | 12       | 1.84(2)                   | 2.79(2)                     | –                                          | –                                            |
| $TM-F^{[b]}$                      | 45       | 1.85(3)                   | 2.80(2)                     | –                                          | –                                            |
| $BF_4^-$                          | 34       | 2.01(3)                   | 2.94(3)                     | –                                          | –                                            |
| $PF_6^-$                          | 18       | 2.08(3)                   | 2.98(3)                     | –                                          | –                                            |
| $C-F$                             | 5        | 2.19(–)                   | 3.07(–)                     | –                                          | –                                            |
| $Cl^-$                            | 1013     | 2.245(3)                  | 3.196(3)                    | 2.10–2.46                                  | 3.06–3.38                                    |
| $TM-Cl^{[b]}$                     | 232      | 2.349(9)                  | 3.272(8)                    | 2.15–2.62                                  | 3.11–3.51                                    |
| $C-Cl$                            | 30       | 2.77(5)                   | 3.62(5)                     | –                                          | –                                            |
| $Br^-$                            | 233      | 2.415(8)                  | 3.350(7)                    | 2.25–2.66                                  | 3.21–3.61                                    |
| $TM-Br^{[b]}$                     | 17       | 2.56(4)                   | 3.47(4)                     | –                                          | –                                            |
| $C-Br$                            | 1        | 2.83(–)                   | 3.66(–)                     | –                                          | –                                            |
| $I^-$                             | 47       | 2.68(1)                   | 3.61(1)                     | –                                          | –                                            |
| $TM-I$                            | 6        | 2.90(8)                   | 3.74(6)                     | –                                          | –                                            |
| <i><math>\pi</math> acceptors</i> |          |                           |                             |                                            |                                              |
| $Ph$                              | 25       | 2.50(4)                   | 3.38(4)                     | –                                          | –                                            |
| $C\equiv C$                       | 2        | 2.51(–)                   | 3.35(–)                     | –                                          | –                                            |
| $C=C$                             | 20       | 2.73(4)                   | 3.57(4)                     | –                                          | –                                            |
| $Py$                              | 4        | 2.79(–)                   | 3.72(–)                     | –                                          | –                                            |

[a] The “95 % ranges” of the  $H\cdots A$  and  $O_W\cdots A$  distances include 95 % of the hydrogen bonds. They are given only if  $n > 50$ . For distributions without a pronounced maximum, the 2.5th percentile is given instead of the central 95 %. [b] TM = transition metal atom.

Mean distances are listed in Table 3 for fairly linear  $X-H \cdots O_W$  hydrogen bonds ( $W$  = water molecule) from 47  $X-H$  donor types ( $X = O, N, S$ , and  $C$ ). If one uses the ranking of distances to define a “donor strength” of  $X-H$ , one finds a general ranking  $O-H > N-H > S-H > C-H$ . These are only rough categories, however, with strong internal variations. Hydrogen bonds of the strongest  $C-H$  types ( $Cl_3CH$ ,  $C \equiv CH$ ) are clearly shorter on average than those with the weakest  $N-H$  donors ( $C_{sp^2}-NH_2$ ,  $N-NH_2$ ). The ranking within the  $X-H$  groups follows a simple rule: basically, the donor strength is increased by neighboring electron-withdrawing groups and reduced by electron-donating groups. In consequence, the ranking of  $O-H$  donor strengths is  $H_3O^+ > O=C-OH > Ph-OH > C_{sp^3}-OH > H_2O > OH^-$ . The difference in mean bond lengths  $D$  within this sequence amounts to over 0.7 Å! Remember, however, that each of the lines in Table 3 corresponds to a broad histogram (such as in Figure 11a). The corresponding 95 % ranges are normally over 0.3 Å broad (last two columns in Table 3), which implies there are large overlapping regions of hydrogen bond geometries between most donor types.

An analogous list is given in Table 4 for water  $O_W-H \cdots A$  hydrogen bonds with 61 different acceptor types ( $A = O, N, S, Se$ , halogen,  $\pi$  system). It is clear that acceptor strengths are increased by neighboring electron-donating groups and reduced by electron-withdrawing groups. The ranking of strengths for  $O$  acceptors is  $^-OH > ^-COO^- > H_2O > C_{sp^3}-OH > Ph-OH > C-NO_2 > M-CO$ , with mean bond lengths varying by 0.6 Å. A broad range of acceptor strengths is also observed for fluorine:  $F^- > M-F > BF_4^- > C-F$ .

Tables 3 and 4 summarize the data for  $H_2O$  as an acceptor and a donor, respectively. A more comprehensive picture would require data for *all* donor–acceptor combinations. The  $X-H$  and  $A$  groups from Tables 3 and 4 would fill a  $48 \times 61$  matrix with almost 3000 entries, too many to be discussed in practice. Sections of this matrix have been published for the special cases of  $X-H \cdots Hal^-$ ,<sup>[60]</sup>  $C-H \cdots O$  and  $C-H \cdots N$ ,<sup>[83]</sup> and  $C-H \cdots \pi$ <sup>[84]</sup> hydrogen bonds.

General properties of donor–acceptor matrices are best discussed with smaller example matrices, such as those in Tables 5 and 6. Part of the  $O-H \cdots O$  matrix with four donors, and four acceptors that cannot act as donors simultaneously ( $C=O$ , etc.) is shown in Table 5. The ranking of the donor strength is here independent of the acceptor, and the ranking of the acceptor strength is independent of the donor.

A related matrix is shown in Table 6 for four kinds of  $O-H$  groups acting as donor as well as acceptor. Here, the important observation is that strong donors are weak acceptors, and vice versa. The  $O-H$  group of the carboxylic acid, for

Table 6. Intermolecular  $O-H \cdots O$  hydrogen bonds: Donor–acceptor matrix with  $O-H$  groups that can act as donors as well as acceptors (mean  $O \cdots O$  distances in Å, sample size in square brackets). (For this article database information was retrieved.<sup>[10a]</sup>)

| Donor           | Acceptor        |                 |                |              |
|-----------------|-----------------|-----------------|----------------|--------------|
|                 | H–O–H           | $C_{sp^3}$ –O–H | Ph–O–H         | (O=C)–O–H    |
| H–O–H           | 2.825(2) [2505] | 2.831(4) [757]  | 2.89(1) [89]   | 2.94(3) [35] |
| $C_{sp^3}$ –O–H | 2.753(3) [763]  | 2.792(2) [4249] | 2.84(1) [94]   | 2.89(–) [3]  |
| Ph–O–H          | 2.679(7) [144]  | 2.721(7) [145]  | 2.807(6) [305] | 2.97(–) [2]  |
| O=C–O–H         | 2.591(4) [244]  | 2.646(6) [162]  | 2.69(2) [8]    | –            |

example, is a very strong donor but a very poor acceptor. The water molecule is a good acceptor but only a moderate donor.

The distance properties  $d$  and  $D$  discussed above might indicate that donor and acceptor “strengths” are integral properties of any group  $X-H$  or  $A$ . The shortest hydrogen bonds could then be made by simply combining the strongest donor with the strongest acceptor. Such a view is correct in the electrostatic regime of hydrogen bonds, namely, for those defined as “moderate” and “weak” in Section 2.10. It is *not* correct, however, for strong hydrogen bonds, where the laws of covalent bonding and of proton transfer phenomena become dominant (see Section 7). For example, if one tries to make a short  $O-H \cdots O$  bond by simply combining the strongest donor from Table 3 ( $H_3O^+$ ) with the strongest acceptor in Table 4 ( $OH^-$ ) a proton transfer will occur ( $H_2O^+-H \cdots OH^- \rightarrow H_2O \cdots H-OH$ ) which leads to a moderate hydrogen bond between water molecules. Similarly, it would be wrong to assume a strict relationship between hydrogen bond length and energy. Hydrogen bonds involving ions generally have a higher dissociation energy than those between neutral molecules (this is a trivial consequence of the Coulombic attraction of the net charges), but need not have much shorter bond lengths (see, for example, the charged acceptor  $NO_3^-$  in Table 4, with a long average  $O \cdots O_W$  distance of 2.97 Å).

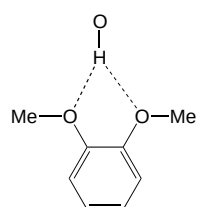
### 3.4. Bifurcated Hydrogen Bonds

In a multifurcated hydrogen bond, a donor forms hydrogen bonds with more than one acceptor simultaneously (Scheme 2). Multifurcated hydrogen bonding requires a high density of acceptors, at least locally (Scheme 2). Over 25 % of all  $O-H \cdots O$  hydrogen bonds in carbohydrates are multifurcated, and this fraction is even higher in amino acids.<sup>[6]</sup> Proteins also contain multifurcated hydrogen bonds in large numbers.<sup>[85]</sup> It is not always easy to show that all components are bonding, in particular if angles  $\theta$  are small and/or some of the putative acceptors are forced by stereochemistry to be close to the donor. For a number of bifurcated bonds, however, bond paths in the theoretical electron density have been shown for both components.<sup>[86]</sup>

As a consequence of their geometry, certain chemical groups are involved in these interactions with a particularly high frequency. A typical example of the *ortho*-dimethoxyphenyl group is shown in Scheme 4. In a database analysis,<sup>[10c]</sup> 31  $O-H \cdots O$  hydrogen bonds with this group were found, and of these, only 10 involve just one acceptor, whereas 21

Table 5. Intermolecular  $O-H \cdots O$  hydrogen bonds with acceptors that cannot act as donors (mean  $O \cdots O$  distances in Å, sample size in square brackets). (Database information was retrieved for this article.<sup>[10a]</sup>)

| Donor          | Acceptor        |                 |                |              |
|----------------|-----------------|-----------------|----------------|--------------|
|                | $^-COO^-$       | $R_2C=O$        | $C-O-C$        | $C-NO_2$     |
| O=C–OH         | 2.544(3) [421]  | 2.644(1) [1491] | 2.72(2) [29]   | 2.80(–) [3]  |
| Ph–OH          | 2.65(1) [57]    | 2.734(5) [412]  | 2.812(2) [58]  | 2.96(3) [11] |
| $C_{sp^3}$ –OH | 2.736(5) [354]  | 2.824(2) [2567] | 2.885(4) [764] | 3.00(1) [74] |
| H–O–H          | 2.807(3) [1035] | 2.840(2) [2485] | 2.910(7) [254] | 3.04(2) [57] |



Scheme 4. Example of a functional group with a strong tendency to accept bifurcated hydrogen bonds (21 out of 31 hydrogen bonds found in a CSD analysis were bifurcated).<sup>[10c]</sup>

(=68%) are bifurcated. Of the latter, 8 are almost symmetric, with the two  $\text{H}\cdots\text{O}$  distances differing by less than 0.2 Å.

A strongest ("major") component can be clearly identified in most multifurcated hydrogen bonds, but not always. Even trifurcated hydrogen bonds occur occasionally with a fairly symmetric geometry. The triethanolammonium cation, for example, is always found in crystal structures in very similar bowl-shaped conformations with the three hydroxy O atoms converging toward the  $\text{N}^+\text{--H}$  donor (Figure 12).<sup>[77, 87]</sup>

Frequently, the two acceptors of a bifurcated hydrogen bond are of different types,  $\text{A}_1$  and  $\text{A}_2$ . If one is much weaker than the other (such as with  $\text{A}_1 = \text{O}$ ,  $\text{N}$ , and  $\text{A}_2 = \text{Hal--C}$ ,  $\pi$ , etc.) it may be difficult to assess if it is actually of any structural importance. However, numerous examples of bifurcated hydrogen bonds have been found with a strong and a weak acceptor, occasionally even with the interaction geometry more favorable to the weaker acceptor (Scheme 5).<sup>[88]</sup>

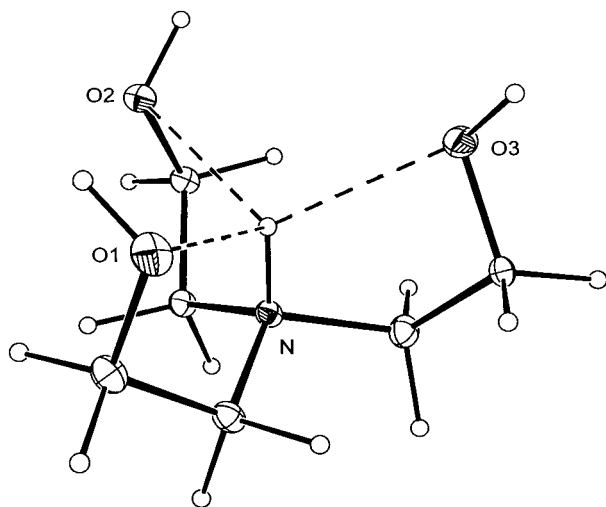
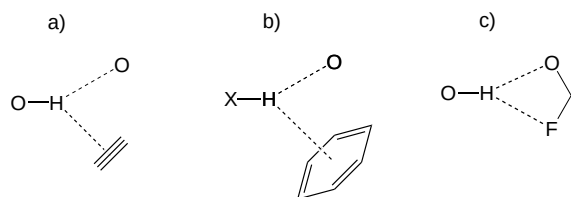


Figure 12. Trifurcated hydrogen bond in the triethanolammonium cation as seen in the neutron diffraction crystal structure of the dihydrated tetraphenylborate salt.<sup>[87]</sup> The three  $\text{N}^+\text{--H}\cdots\text{O}$  hydrogen bonds have very similar geometries ( $\text{H}\cdots\text{O} = 2.14\text{--}2.35$ ,  $\text{N}\cdots\text{O} = 2.71\text{--}2.86$  Å,  $\text{N--H}\cdots\text{O} = 108\text{--}112^\circ$ ).



Scheme 5. Examples of bifurcated hydrogen bonds with a strong and a weak acceptor: a) with O and  $\text{C}\equiv\text{C}$  acceptors;<sup>[8, 88a,b]</sup> b) with O and Ph acceptors;<sup>[80, 88c]</sup> c) with O and  $\text{F--C}$  acceptors.<sup>[88d]</sup>

### 3.5. $\text{H}\cdots\text{H}$ Contacts

The matter of short repulsive  $\text{H}\cdots\text{H}$  contacts is often overlooked when interpreting hydrogen bond geometries. If a hydrogen bond is formed between two  $\text{X--H}$  groups (or an  $\text{X--H}$  and an  $\text{Y--H}$  group), the two may be roughly in-line so that the H atoms are far apart from each other, but they may also form an angle in such a way that the H atoms approach quite closely (Figure 13). In database analyses of inorganic<sup>[89]</sup> and organic<sup>[90]</sup> crystal structures, a lower limit of 2.05 Å was

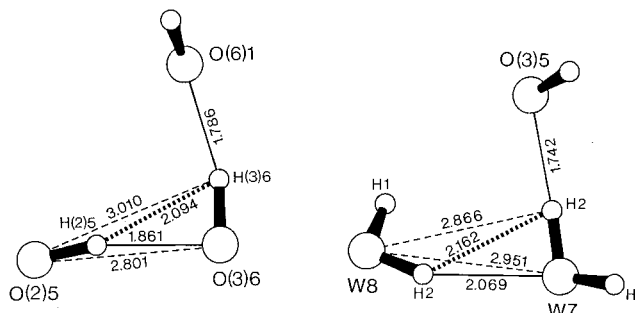
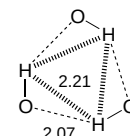
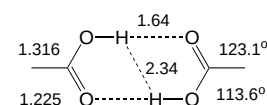


Figure 13. Typical examples of short  $\text{H}\cdots\text{H}$  contacts in  $\text{O--H}\cdots\text{O--H}$  hydrogen bonds found by neutron diffraction studies of carbohydrates.<sup>[90]</sup>

found for  $\text{H}\cdots\text{H}$  contacts in such configurations. This does not affect linear hydrogen bonded chains very much, but it imposes serious constraints on the geometry of circular arrays of hydrogen bonds. Short  $\text{H}\cdots\text{H}$  contacts cannot be avoided in rings of three hydroxy groups or water molecules in particular (Scheme 6). They force angles  $\theta$  to be very bent, and probably are the reason why these rings are very rare. Fairly short  $\text{H}\cdots\text{H}$  contacts occur also in cyclic hydrogen-bonded dimers and destabilize such arrays, for example, in the carboxylic acid dimer with  $\text{H}\cdots\text{H}$  contacts of about 2.34 Å (Scheme 7) and many related patterns.



Scheme 6. Short  $\text{H}\cdots\text{H}$  contacts are unavoidable in rings of three  $\text{O--H}\cdots\text{O}$  hydrogen bonds. The mean geometry in crystals is:  $d = 2.07(3)$  Å,  $D = 2.89(2)$  Å,  $\theta = 143(2)^\circ$ ,  $\text{H}\cdots\text{H} = 2.21(3)$  Å.<sup>[10d]</sup>



Scheme 7. Mean geometry of the carboxylic acid dimer in crystals.<sup>[10e]</sup> Note the short destabilizing  $\text{H}\cdots\text{H}$  contact. The mean  $\text{O}\cdots\text{O}$  distance is 2.644 Å.

### 3.6. Influence on Covalent Geometry

Hydrogen bonding affects the covalent geometry of the molecules involved. The lengthening of the covalent  $\text{X--H}$  bond was already described in the 1950s,<sup>[91]</sup> and the correlation of the  $\text{O--H}$  and  $\text{H}\cdots\text{O}$  distances in  $\text{O--H}\cdots\text{O}$  interactions has been studied many times with increasing precision. The current correlation based on low-temperature neutron diffraction data is shown in Figure 14a.<sup>[92]</sup> The  $\text{O--H}$  bond continuously elongates with decreasing  $\text{H}\cdots\text{O}$  distance until a symmetric geometry  $\text{O--H--O}$  is reached at an  $\text{O}\cdots\text{O}$  separation of about 2.39 Å.

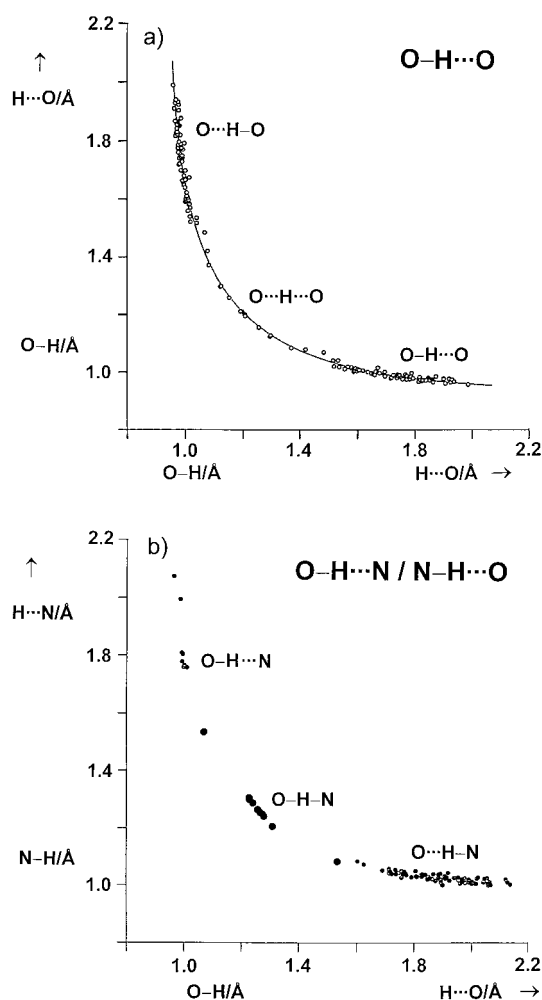


Figure 14. Lengthening of the X-H bond in X-H...A hydrogen bonds. a) Correlation of O-H and H...O distances in O-H...O hydrogen bonds.<sup>[92]</sup> The plot is symmetrized with respect to the two O atoms.<sup>[31b]</sup> b) Correlation of N-H with H...O bond lengths and O-H with H...N bond lengths.<sup>[93]</sup> The right branch shows N-H...O, and the left branch shows O-H...N hydrogen bonds. Both plots are based on neutron diffraction data.

The correlation is perfectly smooth. There is no indication of a critical distance at which the hydrogen bond switches from one interaction type to another. The elongation is in the range 0.02–0.08 Å for moderate hydrogen bonds (Table 2), but it is up to 0.25 Å for strong ones. The analogous scatter plot for N-H...O and O-H...N hydrogen bonds also shows a smooth correlation (Figure 14b),<sup>[93]</sup> with the geometrically symmetric bond occurring at an N...O distance of about 2.50 Å. An alternative way to illustrate the elongation of X-H bonds is to draw X-H and H...A distances as a function of the X...A separation, as shown in Figure 15 for the example of O/N-H...N/O bonds.

Lengthening of the X-H bond has been found for many other kinds of X-H...A hydrogen bonds, and seems typical of hydrogen bonding. The effect has been described for N-H...N,<sup>[94]</sup> O-H...S,<sup>[36]</sup> N-H...S,<sup>[36]</sup> O-H...Cl,<sup>[36]</sup> N-H...Cl,<sup>[36]</sup> and C-H...O<sup>[95]</sup> interactions, although the full range of geometries has been explored only for the types shown in Figure 14. For some special systems,

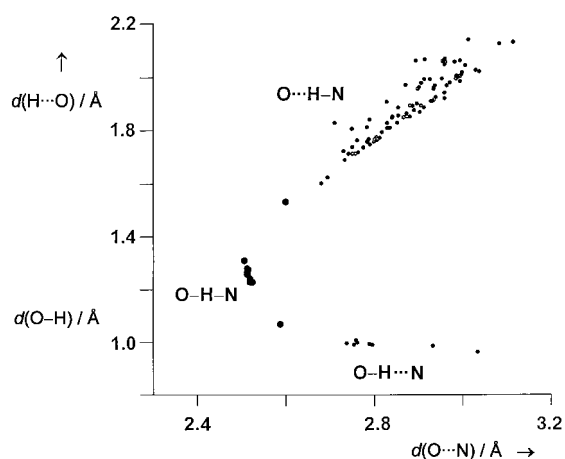
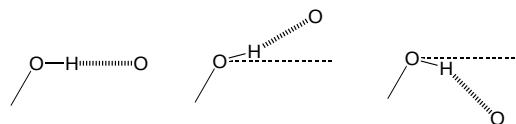


Figure 15. Correlation of O-H and H...O bond lengths with the O...N distance in O/N-H...N/O hydrogen bonds (neutron diffraction data).<sup>[93]</sup>

quantum chemical calculations predict shortening, not lengthening, of the X-H bond,<sup>[55, 96]</sup> but there is no consensus on this among theorists<sup>[27]</sup> and experimental structural proof is still lacking.

X-H...A hydrogen bonding also affects the angles at X (Scheme 8). For the example of  $\text{NH}_3^+ \cdots \text{Cl}^-$  hydrogen bonds, the bending of the C-N-H angle as a function of the



Scheme 8. Bending of the X-O-H angle in O-H...A hydrogen bonds.

C-N<sup>+</sup>...Cl<sup>-</sup> coordination angle is shown in Figure 16.<sup>[36]</sup> The change in the angle between the covalent bonds follows that in the coordination angle, but is much smaller. Related plots have been given for the bending of C-O-H groups, and for the opening and narrowing of the water angle by O-H...O and O-H...Cl<sup>-</sup> hydrogen bonds.<sup>[97]</sup> The bending typically amounts to only a few degrees, which is easy to see with neutron diffraction, but difficult to discern in X-ray diffraction studies.

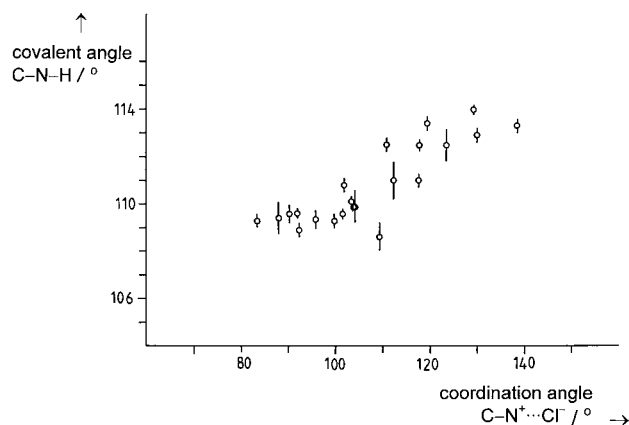
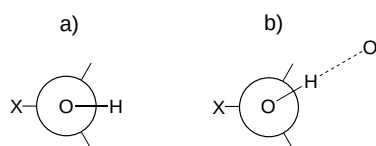


Figure 16. Bending of the C-N-H angle in N-H...Cl<sup>-</sup> hydrogen bonds ( $\text{NH}_3^+$  donors, neutron diffraction data).<sup>[36]</sup>

Torsional angles in molecular fragments may be influenced by hydrogen bonds to a degree that depends on the height of the torsional barrier between energy minima. The O–H bond in a hydroxy group  $C_{sp^3}$ –OH, for example, prefers to be staggered with respect to the substituents at C (Scheme 9a). In



Scheme 9. Effect of hydrogen bonding on torsional angles. a) Free, and b) hydrogen-bonding hydroxy group.

crystal structures, on the other hand, the torsion angle around C–O takes any value. If this angle is plotted against the  $X-C-O\cdots O$  dihedral coordination angle, it is seen that the O–H vector is always rotated towards the acceptor, even into an eclipsed orientation (Scheme 9b and Figure 17).<sup>[98]</sup> The

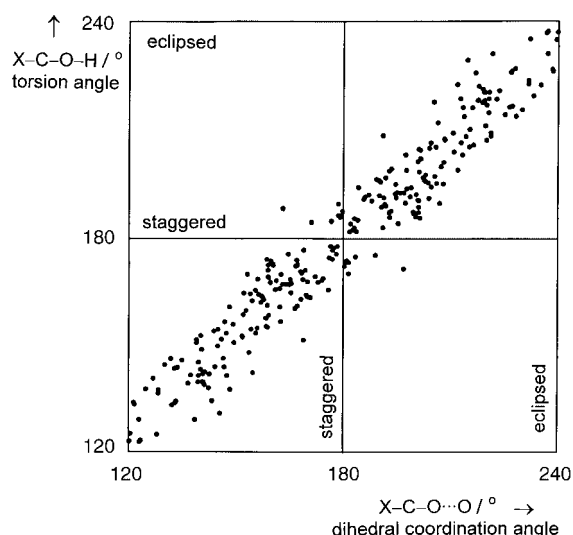


Figure 17. Rotation of hydroxy groups away from a staggered conformation as a result of hydrogen bonding: the  $X-C-O-H$  torsion angle adjusts to the  $X-C-C\cdots O$  dihedral coordination angle.<sup>[98]</sup>

same kind of analysis can be performed for methyl groups of the type  $C_{sp^3}$ –CH<sub>3</sub> involved in  $C-H\cdots O$  interactions. In this case, the torsional barrier is far too high (typically 3–5 kcal mol<sup>−1</sup>) to reach the eclipsed conformation. Nevertheless, rotations of up to 10–15° from the ideally staggered conformations have been detected, which corresponds to a displacement of the H atoms by 0.2 Å from their idealized positions.<sup>[98]</sup> A single case of an eclipsed methyl group associated with three  $C-H\cdots O$  bonds has been reported,<sup>[99]</sup> but theoretical calculations show that the torsional barrier in this particular molecule is dramatically reduced to about 1.5 kcal mol<sup>−1</sup>.<sup>[100]</sup>

The effects discussed above concern distances and angles directly involving the H atom. There are also changes in the covalent geometry of the non-hydrogen molecular skeleton of

both participating molecules. These effects are modest for moderate, and negligible for weak hydrogen bonds, but they can become very large for strong ones. In a  $C-O-H\cdots O=C$  hydrogen bond, for example, the C–O bond is shortened and the O=C bond is lengthened compared to the free molecules.<sup>[101]</sup> In the extreme case of the symmetric hydrogen bond, the two C–O bond lengths become identical,  $C-O\cdots H\cdots O-C$ . Figure 18 shows that the difference of the two C–O distances depends linearly on the  $O\cdots O$  distance (note that the effect is already quite large with  $O\cdots O=2.6$  Å).<sup>[46]</sup> Carboxylate groups that accept one hydrogen bond become unsymmetric, and the C–O bond involving the accepting O atom becomes several hundredths of an Å longer than the other one (see, for example, ref. [102]).

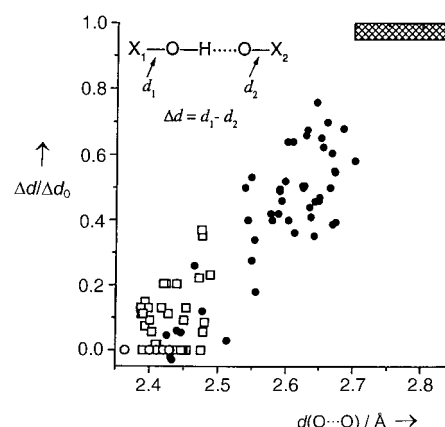


Figure 18. Effect of  $C-O-H\cdots O=C$  hydrogen bonding on C–O bond lengths. The quantity  $\Delta d$  is the difference between the donor C–O and the acceptor  $O=C$  bond length ( $d_0$  = value for fragments free of hydrogen bonding; squares: combination of acid and complementary base; dots: resonance-assisted hydrogen bonds).<sup>[46]</sup>

All these correlations can be easily rationalized if they are interpreted as mapping a proton-transfer reaction. The geometry of the donor molecule changes in the direction of the deprotonated species, and the geometry of the accepting molecule changes in the direction of a protonated one. This has been nicely demonstrated by suitable chemical variations of substituted phenol–amine adducts<sup>[103]</sup> to form molecular or ionic adducts, and also into intermediate cases.<sup>[104]</sup> A plot of the phenolic C–O bond length against the  $O\cdots N$  distance gives the correlation shown in Figure 19. The data in the upper right corner show normal phenolic C–O bond lengths of around 1.34 Å, and are associated with moderate strength  $O-H\cdots N$  hydrogen bonds. As the hydrogen bonds become shorter, the H atom is gradually abstracted and the C–O bond shortens. The data in the bottom right corner show a phenolate C–O bond length of 1.25 Å, and are associated with ionic hydrogen bonds  $N^+-H\cdots O-C$ . The symmetric situation  $C-O\cdots H\cdots N$  is reached at an  $N\cdots O$  distance of about 2.50 Å.

A related effect is observed for the  $C\sim N\sim C$  angle in pyridine molecules (Figure 20).<sup>[105]</sup> The neutral pyridine molecule has an angle at the nitrogen atoms of 116.6°,<sup>[105]</sup> whereas in pyridinium ions they are widened to 121–123° (for example, 122.6° in  $Py\cdot HCl\cdot HCl$ ).<sup>[106]</sup> This angle in  $O-H\cdots N$

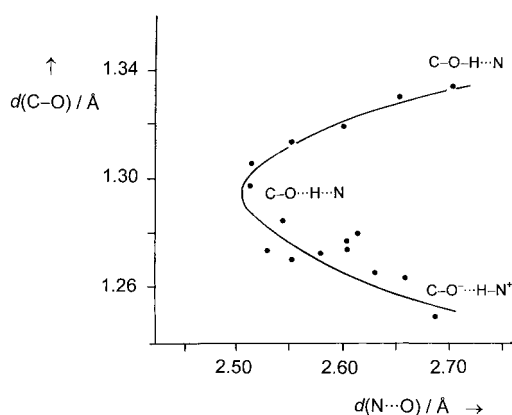


Figure 19. Effect of hydrogen bonding on the phenolic C–O bond length. Data from adducts of phenols and amines.<sup>[103]</sup>

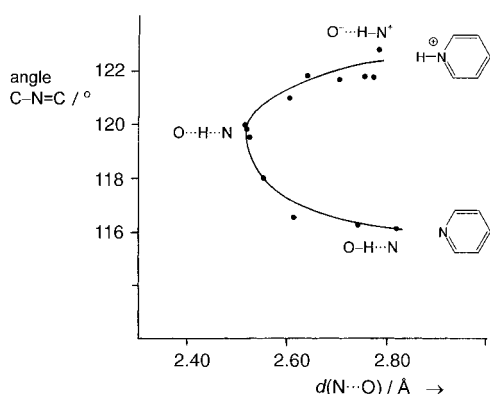


Figure 20. Effect of hydrogen bonding on the C–N=C angle in pyridine.<sup>[100]</sup>

hydrogen bonds is increasingly widened as the hydrogen bond becomes shorter (lower branch of the curve), and it is narrowed in  $N^+-H\cdots O$  hydrogen bonds as the bond becomes shorter. The branches meet again at  $O\cdots N = 2.50$  Å, with an angle at N of  $120^\circ$ . Changes in covalent geometry also play an important role in the case of resonance-assisted hydrogen bonding (see Section 4.2).

### 3.7. H/D Isotope Effects

The H/D isotope effect is a curious matter in the area of hydrogen bonds. In the classical Ubbelohde effect, hydrogen bond lengths slightly increase upon deuteration.<sup>[107]</sup> This is thought to be a result of the lower zero-point vibrational energy of the O–D relative to the O–H bond, which makes the O–D bond more stable. In consequence, D is more difficult to abstract from O than H, and the hydrogen bonds are weaker. The Ubbelohde effect has been examined experimentally for only a few O–H/D $\cdots$ O pairs. From a recent survey it appears that the isotope effect is strongest in the  $O\cdots O$  distance range 2.5–2.6 Å (Figure 21).<sup>[108]</sup> It is much smaller for long hydrogen bonds, and about zero for very short ones (possibly, even negative values are allowed). The details of the effect are as yet unexplained.

Isotope exchange occasionally leads to more severe structural changes. A well-studied example is trifluoroacetic acid

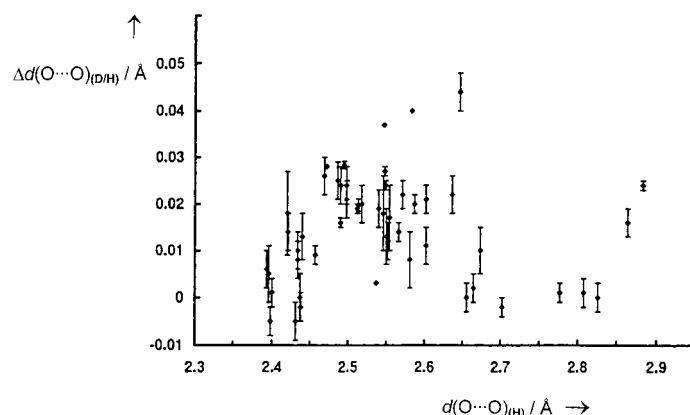


Figure 21. H/D isotope effect on hydrogen bond lengths. The difference of  $O\cdots O$  distances in pairs of D and H compounds is plotted against the  $O\cdots O$  distance of the H compound. A value of  $\Delta > 0$  means that the hydrogen bond in the D compound is longer.<sup>[108]</sup>

tetrahydrate, which is cationic in the protonated form,  $F_3C-COO^-\cdot 3H_2O\cdot H_3O^+$ , whereas it becomes molecular when deuterated,  $F_3C-COOD\cdot 4D_2O$ .<sup>[109]</sup>

## 4. Non-Additivity

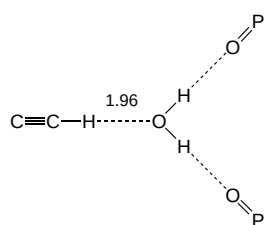
Many properties of  $n$  interconnected hydrogen bonds are not just the sum of those of  $n$  isolated bonds. Two principal mechanisms are responsible for this non-additivity, and both operate by mutual polarization of the involved groups.

### 4.1. $\sigma$ -Bond Cooperativity

If an  $X^{\delta-}-H^{\delta+}$  group forms a hydrogen bond  $X^{\delta-}-H^{\delta+}\cdots A^{\delta-}$ , it becomes more polar. The same is true if it accepts a hydrogen bond,  $Y^{\delta-}-H^{\delta+}\cdots X^{\delta-}-H^{\delta+}$ . Thus, in a chain with two hydrogen bonds,  $Y-H\cdots X-H\cdots A$ , both become stronger. The effect is often called “ $\sigma$ -bond cooperativity”,<sup>[6]</sup> since the charges flow through the X–H  $\sigma$  bonds, but the terms “polarization-enhanced hydrogen bonding”<sup>[110]</sup> or “polarization-assisted hydrogen bonding” (as opposed to resonance-assisted hydrogen bonding)<sup>[46]</sup> have also been proposed. Model calculations on moderate strength hydrogen bonds yield typical energy gains of around 20% relative to isolated interactions.<sup>[7]</sup>

$\sigma$ -Bond cooperativity drives the clustering of polar groups. In the condensed phases, this leads to formation of  $X-H\cdots X-H\cdots X-H$  chains and rings, in particular for  $X=O$ , but also for  $X=N$  or  $S$ . If double donors (such as  $H_2O$ ) and/or double acceptors are involved, they can interconnect chains and rings to form complex networks. The topology of such networks has been documented in great detail for the O–H-rich carbohydrates.<sup>[5, 111, 112]</sup>

An unusual array cooperative  $\sigma$ -bond is shown in Scheme 10. The polarity of the water molecule is greatly enhanced by two hydrogen bonds donated to strong  $O=P$

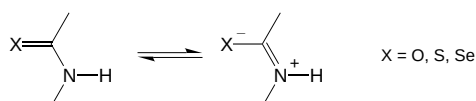


Scheme 10. A very short  $\text{C}\equiv\text{C}-\text{H}\cdots\text{O}$  hydrogen bond.  $\sigma$ -Bond cooperativity enhances the acceptor strength of the water molecule ( $\text{C}\cdots\text{O} = 3.02 \text{ \AA}$ ).<sup>[113]</sup>

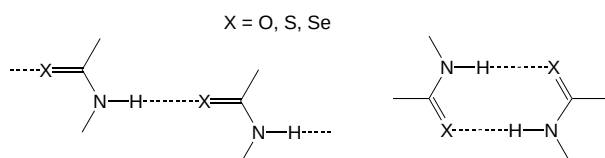
acceptors, so that the accepted  $\text{C}\equiv\text{C}-\text{H}\cdots\text{O}$  hydrogen bond becomes very short, in fact the shortest ever found for an acetylenic donor.<sup>[113]</sup>

#### 4.2. $\pi$ -Bond Cooperativity or Resonance-Assisted Hydrogen Bonding (RAHB)

$\text{X}-\text{H}$  groups may also be polarized by charge flow through  $\pi$  bonds. For example, an amide  $\text{N}-\text{H}$  group becomes a stronger donor if the amide  $\text{O}$  atom accepts a hydrogen bond,  $\text{X}-\text{H}\cdots\text{O}=\text{C}-\text{N}-\text{H}$ . This results because the zwitterionic resonance form is stabilized (Scheme 11). The same effect occurs in thio- and selenoamides.<sup>[8]</sup> Amide units, as a result of their dual donor and acceptor capacity, often form hydrogen-bonded chains or rings (such as in protein secondary structure; Scheme 12). Since the polarization occurs through  $\pi$  bonds, the effect is often called  $\pi$ -bond cooperativity.<sup>[6]</sup>

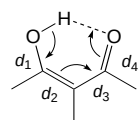


Scheme 11. Resonance forms of amide, thioamide, and selenoamide groups. The neutral form is always dominating, but the weight of the zwitterionic form is increased by accepted as well as by donated hydrogen bonds.



Scheme 12. Chains and rings as formed by amides, thioamides, and selenoamides through the  $\pi$ -bond cooperativity.

On the basis of studies of intramolecular hydrogen bonds in  $\beta$ -diketone enolates Gilli et al. call this effect “resonance-assisted hydrogen bonding” (RAHB).<sup>[114]</sup> A short hydrogen bond in the  $\beta$ -diketone enolates is associated with a charge flow through the system of conjugated double bonds (Scheme 13). The  $\text{C}-\text{O}$  and  $\text{C}-\text{C}$  bonds gain partial double bond character and are shortened, whereas the  $\text{C}=\text{O}$  and  $\text{C}=\text{C}$



Scheme 13. Resonance-assisted hydrogen bonding (RAHB) in  $\beta$ -diketones enolates.<sup>[114]</sup>

bonds are weakened correspondingly. If a delocalization parameter  $Q = (d_1 - d_4) + (d_3 - d_2)$  is plotted against the  $\text{O}\cdots\text{O}$  distance (Figure 22) it is seen that the delocalization systematically increases with a shortening of the hydrogen bond length. In the extreme case of a symmetric position of the  $\text{H}$  atom,  $Q$  is zero and the entire fragment becomes symmetric. Completely analogous effects operate in

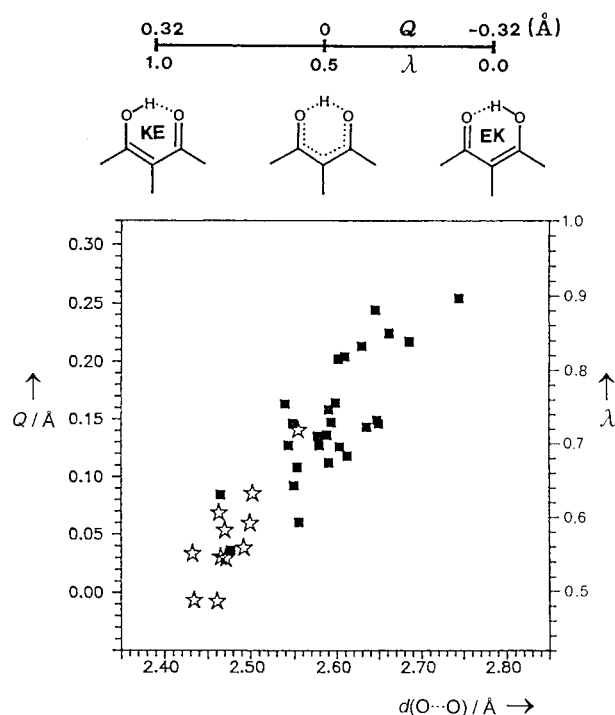
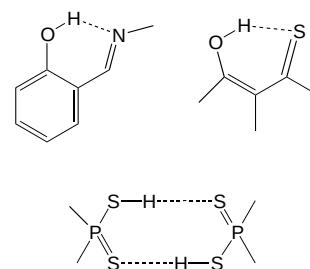


Figure 22. Resonance-assisted hydrogen bonding (RAHB) in enolones according to Gilli et al.<sup>[114]</sup> The parameter  $Q$  measuring the degree of  $\pi$  delocalization decreases with decreasing  $\text{O}\cdots\text{O}$  distance ( $Q = 0$  indicates a completely delocalized  $\pi$  system). Stars represent intramolecular, and squares represent intermolecular hydrogen bonds.

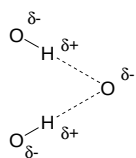
longer chains of conjugated double bonds with intra- and also intermolecular hydrogen bonds.<sup>[115]</sup> The best known example is the carboxylic acid dimer (Scheme 7). Any other suitable donor–acceptor pair connected by a resonant  $\pi$  system will also show the effect. The cases  $\text{N}-\text{H}\cdots\text{O}$  and  $\text{O}-\text{H}\cdots\text{N}$ ,<sup>[116]</sup>  $\text{N}-\text{H}\cdots\text{S/Se}$ ,<sup>[8]</sup>  $\text{O}-\text{H}\cdots\text{S}$ ,<sup>[117]</sup> and  $\text{S}-\text{H}\cdots\text{S}$ <sup>[118]</sup> (Schemes 12 and 14) illustrate the variety, for which experimental evidence of the  $\pi$ -bond cooperativity is available.



Scheme 14. Examples of  $\pi$ -bond cooperative (or resonance-assisted) hydrogen bonds other than  $\text{O}-\text{H}\cdots\text{O}$ . Further examples are given in Scheme 12.

#### 4.3. Anticooperativity

Hydrogen bonds may not only enhance, but also reduce the strengths of each other. This occurs, for instance, at double acceptors where two roughly parallel donor dipoles repel each other (Scheme 15). This effect is probably responsible for the preferences of “homodromic” over “antidromic” cycles of

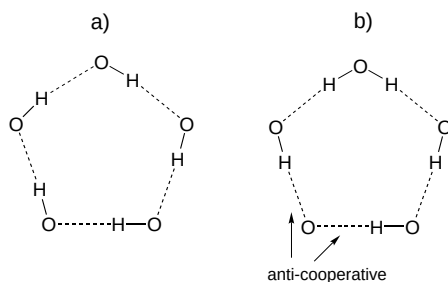


Scheme 15. Anticooperative hydrogen bonds. The two donors represent roughly parallel dipoles that repel each other.

hydrogen bonds (Scheme 16).<sup>[119]</sup> Given their importance for determining intermolecular structures, anticooperative effects have been investigated surprisingly little until now.

## 5. Elongation and Compression by Other Forces

Hydrogen bonds rarely adopt optimal geometry in the condensed states. Crystal-packing forces can easily bend, elongate, and compress them. All these distortions are associated with a weakening of the interaction (typically by only a few tenths of a kcal mol<sup>-1</sup>, and only rarely above 1 kcal mol<sup>-1</sup>). It is a common mistake to believe that in a set of hydrogen bonds between chemically identical groups, the shortest are the strongest. This is *not* the case. In such a set, the strongest hydrogen bonds are those closest to optimal geometry, whereas the shortest may well suffer some compression.



Scheme 16. Cycles of five hydrogen bonds.<sup>[119]</sup> In the preferred “homodromic” arrangement (a) all hydrogen bonds run in the same direction. In the less common “antidromic” arrangement (b) a change of orientation leads to local anticooperativity.

For moderate and strong hydrogen bonds, the hydrogen bond potential is deep enough ( $< -4$  kcal mol<sup>-1</sup>) to keep the distortions relatively limited (Figure 23). The distribution of geometries is narrow enough to show recognizable clustering (see, for example, Figures 7 and 11). Even the most compressed contacts are deep in the bonding regime. For weak hydrogen bonds with dissociation energies of  $\leq 1$  kcal mol<sup>-1</sup>, the entire range of bonding geometries is accessible, and compressed contacts may even be pushed up into the destabilizing regime (Figure 23c).<sup>[8]</sup>

For moderate and strong hydrogen bonds, statistical distance distributions often resemble a Morse potential drawn upside down (compare Figures 1 and 11). It is tempting to interpret such a distance distribution as Boltzmann population of a hydrogen bond potential. This would mean that the distortions of a particular flexible moiety (in this case a hydrogen bond) in the crystal fields of a large number of crystal structures statistically behave the same way as the distortions experienced in the thermal bath of a solution. This view has actually been taken by a number of authors.<sup>[71, 72, 120]</sup> However, quantitative calculations require introduction of quite arbitrary additional assumptions to obtain a reasonable

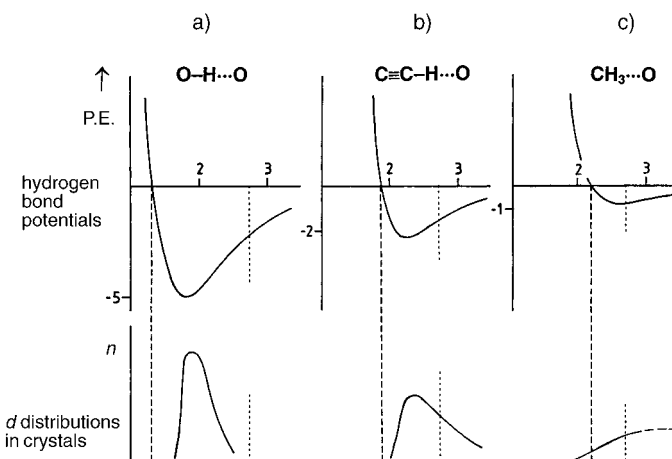


Figure 23. Schematic potential energy curves and distance distributions in crystals for three types of hydrogen bonds. Most hydrogen bond energies are within 1 kcal mol<sup>-1</sup> of the minimum. The destabilizing region is accessible only for very weak hydrogen bond types. The H...O van der Waals separation of 2.7 Å is also indicated, and illustrates that the van der Waals cutoff definition is quite harmless for stronger hydrogen bond types, whereas it omits a large part of the weak hydrogen bonds.<sup>[8]</sup>

fit of model populations with experimental distance distributions.<sup>[120e]</sup> Distance distributions do not resemble Boltzmann population of a Morse potential at all for weak hydrogen bonds (Figure 23).<sup>[8, 81]</sup> Strong criticism was raised by Bürgi and Dunitz, who state that the approach is fundamentally wrong because “an ensemble of structural parameters obtained from chemically different compounds in different crystal structures does not even remotely resemble a closed system at thermal equilibrium and does not therefore conform to the conditions necessary for the application of the Boltzmann distribution”.<sup>[121]</sup>

In Sections 3 and 4, several effects have been discussed that cause a shortening of hydrogen bonds associated with real strengthening (increasing the polarity of X–H or A, cooperativity, etc.). Such effects can be recognized only from large samples of structural data in which effects from random scatter are smaller than the systematic trends. In individual crystal structures, “random distortions” are always chemically rooted although they may be difficult to explain.

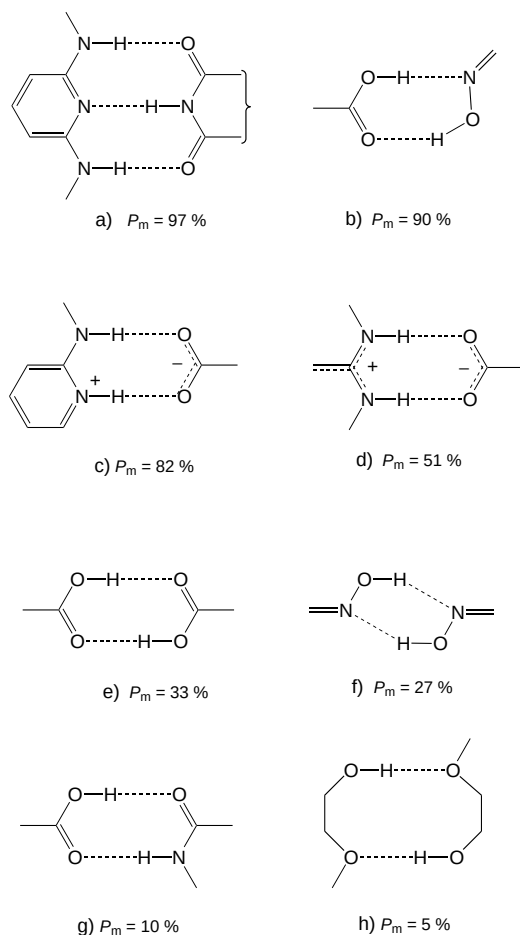
## 6. Probability of Formation

It is difficult to predict whether or not a hydrogen bond between a potential donor X–H and a potential acceptor A in a given system will actually be formed. One can only define a probability of formation, that is, the fraction of X–H...A hydrogen bonds among the number of such hydrogen bonds that could be formed in principle. This is a global property of the sample, averaged over all chemical and structural situations. Nevertheless, the probability of formation is important for judging if a given type of hydrogen bond is general or exotic. Only if a hydrogen bond (or an array of hydrogen bonds) has a reasonably high probability of formation can it be used in rational crystal design (“crystal engineering”). Hydrogen bonds that are formed only occa-



sionally, will be very difficult to control (although they must be understood for rationalizing a crystal structure they are found in).

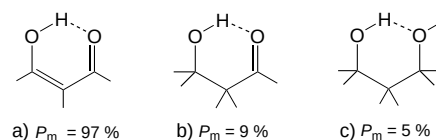
Probabilities of formation can be determined for single hydrogen bonds, as well as for hydrogen bond arrays. In a pioneering investigation work, Allen and co-workers have determined the global probabilities of formation of 75 bimolecular ring motifs;<sup>[122]</sup> part of the results is shown in Scheme 17. The surprisingly poor performance of certain



Scheme 17. Eight examples of intermolecular hydrogen bond motifs with their probability of formation ( $P_m$ ) in crystals.<sup>[122]</sup> Notice that  $P_m$  of the carboxy-oxime heterodimer (b) is much higher than that of the carboxylic acid (e) and oxime homodimers (f).

motifs such as the carboxylic acid dimer can be explained by strong competition of alternative motifs. In a later study, the probability of formation was determined for 50 kinds of intramolecular hydrogen bonds.<sup>[123]</sup> The results for three topologically related rings with O–H $\cdots$ O hydrogen bonds are shown in Scheme 18. The probability of hydrogen bond formation for the  $\beta$ -diketone enolate (Scheme 18a) is close to 100% (because of RAHB), but it is very low for the nonresonant arrangements (Scheme 18b and c).

The formation of hydrogen bonds by the carboxylic acid donor group has been studied in detail.<sup>[124]</sup> Only 29% of all



Scheme 18. Three kinds of intramolecular O–H $\cdots$ O hydrogen bonds with their probability of formation  $P_m$ .<sup>[123]</sup> Array (a) performs far best because it enjoys resonance assistance (Scheme 13). The nonresonant groups in (b) and (c) are conformationally flexible allowing them to avoid formation of the hydrogen bond.

carboxylic acid groups in crystals donate a hydrogen bond to carboxylic acid acceptors (mostly forming the carboxylic acid dimer). The remaining 71% form hydrogen bonds with a great variety of other acceptors. A “relative success” of an alternative acceptor A competing with the carboxylic acid acceptor can be defined as  $\text{succ}(A) = n(\text{OH} \cdots A) / [n(\text{OH} \cdots A) + n(\text{OH} \cdots \text{O}_{\text{carboxy}})]$ . This success rate was found to be over 90% for the strongest acceptors ( $\text{COO}^-$ ,  $\text{P}=\text{O}$ ,  $\text{N}(\text{Py})$ ,  $\text{F}^-$ ,  $\text{Cl}^-$ ). Water is also a very successful competitor ( $\text{succ}(\text{O}_w) = 84\%$ ). The success rates are plotted against mean distances  $D$  for O acceptors in Figure 24. There is a clear correlation

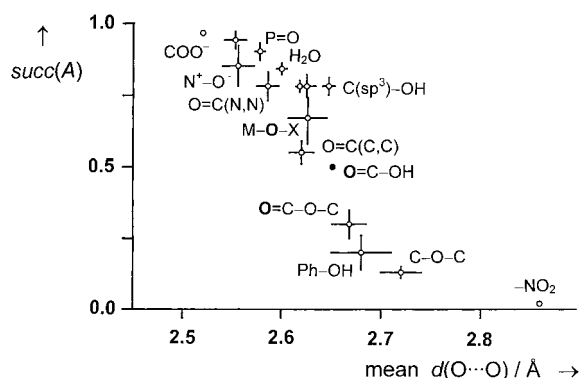
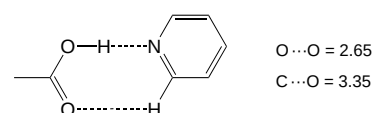


Figure 24. Correlation of the relative success of hydrogen bond acceptors competing for the carboxylic acid donor versus the mean hydrogen bond length.<sup>[124]</sup> Some important acceptors are identified as examples.

between these quantities, and it should be noticed that even weak acceptors such as C–O–C (13%) and  $-\text{NO}_2$  (2%) have a significant chance of attracting the strong carboxylic acid donor. Engineering the carboxylic acid dimer (Scheme 7) clearly requires the absence of successful competitors. If, for example, a pyridyl-N atom is present as a competitor, it is much more likely that a carboxylic acid–pyridine dimer is formed ( $\text{succ}(\text{N}_{\text{Py}}) = 91\%$ ) than a carboxylic acid dimer (Scheme 19).



Scheme 19. Hydrogen-bonded dimer of a carboxylic acid and a pyridyl group; note the C–H $\cdots$ O interaction that is formed in addition to the (much stronger) O–H $\cdots$ N hydrogen bond. Mean geometries found in a CSD analysis ( $n = 32$ ) are for O–H $\cdots$ O:  $d = 1.68(1)$ ,  $D = 2.65(1)$  Å,  $\theta = 171(1)^\circ$ ; for C–H $\cdots$ O:  $d = 2.53(3)$ ,  $D = 3.35(2)$  Å,  $\theta = 127(1)^\circ$ .<sup>[10c]</sup>

Generally, one makes the observation that the probability of formation increases with the number of hydrogen bonds constituting a motif. Whereas “two-point recognition” normally operates only moderately well, three-point recognition is clearly better, and four-point recognition is highly successful.<sup>[125]</sup>

## 7. Very Strong Hydrogen Bonds

Unlike moderate and weak hydrogen bonds, strong hydrogen bonds are quasi-covalent in nature,<sup>[28]</sup> and deserve special discussion. If the hydrogen bond is understood as an incipient proton-transfer reaction, a moderate hydrogen bond represents an early stage of such a reaction, while a strong one represents an advanced stage. It may be noted that from this viewpoint, hydrogen bonds with mainly ionic and little covalent nature are *not* classified as “strong” despite high dissociation energies ( $-\text{NH}_3^+ \cdots \text{Cl}^-$  etc.). Instead, they might be termed ionic interactions with a moderate hydrogen bond formed on top.

Research on strong hydrogen bonds was pioneered by spectroscopists carrying out vibrational studies in solution,<sup>[44, 104, 126]</sup> and was only recently rediscovered by structural chemists. A key finding of spectroscopy is that very strong hydrogen bonds are formed only if the  $\text{p}K_a$  values of the partners are suitably matching. If the  $\text{p}K_a$  values are very different, either a moderate  $\text{X}-\text{H} \cdots \text{Y}$  or an ionic  $\text{X}^- \cdots \text{H}-\text{Y}^+$  hydrogen bond is formed, both of which are not very covalent. The quasi-covalent situation occurs in a certain “critical” range of  $\Delta\text{p}K_a$ , the numerical characteristics of which depend on the particular system (for tabulations, see ref. [126]). The  $\text{p}K_a$  value is a solution property that is not even defined in crystals, and these relationships (and related ones on matching of proton affinities) can not be transferred to the solid state in a general way. A polar environment favors polar forms of a hydrogen bond, and a hydrogen bond that is quasi-covalent in  $\text{CCl}_4$  solution may become ionic in a polar crystal field. In an apolar crystal field, on the other hand, it may possibly remain in a state similar to apolar solution.

In this context, substances are interesting which have an apolar molecular periphery and a single hydrogen bond that is more or less buried inside. The crystal and solution properties of the hydrogen bond in these systems may be surprisingly similar. One example are adducts of pentachlorophenol with pyridines, for which the  $\Delta\text{p}K_a$  value also defines the protonation state in crystals (Figure 25).<sup>[104]</sup>

Strong hydrogen bonds can be grouped into several classes. The combination of acids with their conjugate base is well known (Scheme 20).<sup>[127]</sup> An exact matching of the  $\Delta\text{p}K_a$  values is clear here, and proton transfer leads to a chemically equivalent situation ( $\text{X}-\text{H} \cdots \text{X}^- \rightleftharpoons \text{X}^- \cdots \text{H}-\text{X}$  or  $\text{X}^+-\text{H} \cdots \text{X} \rightleftharpoons \text{X} \cdots \text{H}-\text{X}^+$ ). Gilli and co-workers call these categories “negative” and “positive charge assisted hydrogen bonds”, and compiled numerous examples with structural and, in part, also spectroscopic properties.<sup>[28, 46, 116]</sup> Strong hydrogen bonds of these types form easily, both inter- as well as intramolecularly. Examples of intramolecular hydrogen bonds of this

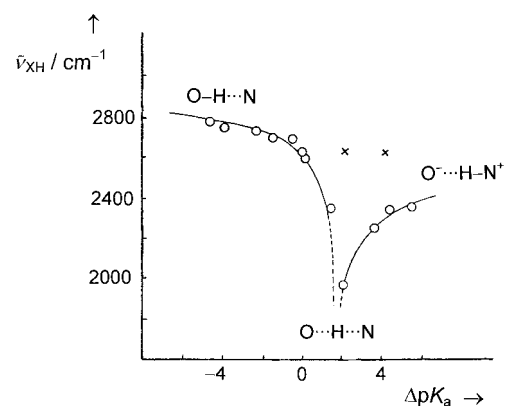
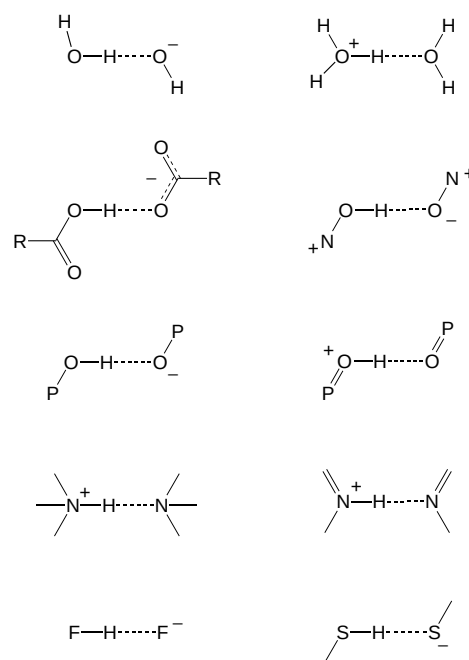


Figure 25. Correlation of  $\Delta\text{p}K_a$  and the IR stretching frequency of crystalline pentachlorophenol–amine adducts. The symbols  $\times$  indicate outliers, presumably caused by crystal-field effects. Very strong hydrogen bonds occur only in a certain “critical” region of  $\Delta\text{p}K_a$  values.<sup>[104a]</sup>



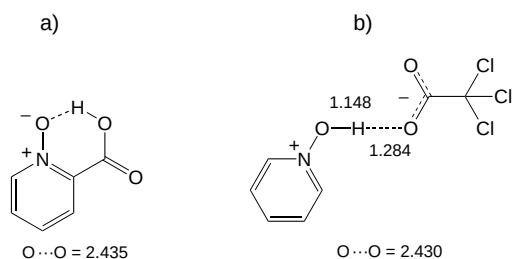
Scheme 20. Examples of strong hydrogen bonds between acids and complementary bases.

kind occur in hydrogenmaleate and hydrogenphthalate anions,<sup>[128]</sup> and in the cations of proton sponges.<sup>[129]</sup>

In systems with resonance-assisted hydrogen bonding (RAHB), such as in the  $\beta$ -diketone enols, proton transfer also leads to a symmetrical situation (Figure 22). RAHB thus provides a mechanism for the formation of strong hydrogen bonds in uncharged systems.<sup>[28]</sup> Substituents attached to the carbon skeleton may disturb the chemical symmetry and thereby weaken the hydrogen bond. For an accurate case study on a particular molecule, the reader is referred to work on the structure of nitromalonamide.<sup>[130]</sup>

Chemically unrelated partners can form strong hydrogen bonds only, if their  $\text{p}K_a$  values match at least roughly. Interesting examples are hydrogen bonds between carboxylic acids and  $N$ -oxides. These systems can be tuned by suitable chemical substitutions to form molecular adducts of the type  $\text{O}=\text{C}-\text{O}-\text{H} \cdots \text{O}^- - \text{N}^+$ , ionic adducts  $-\text{CO}_2^- \cdots \text{H}-\text{O}-\text{N}^+$ , or

the intermediate quasi-covalent type with the H atom placed midway between two O atoms. The latter situation is found intra- and intermolecularly (Scheme 21), with  $\text{O}\cdots\text{O}$  distances almost as short as the shortest possible value of 2.39 Å.<sup>[131, 132]</sup>



Scheme 21. Very short  $\text{O}-\text{H}-\text{O}$  hydrogen bonds between carboxylic acid and  $\text{N}-\text{O}$  groups. a) Intramolecular hydrogen bond in picolinic acid  $\text{N}$ -oxide.<sup>[131]</sup> b) Intermolecular hydrogen bond in the adduct formed between pyridine- $\text{N}$ -oxide and trichloroacetic acid.<sup>[132]</sup> (Numerical values are obtained from a neutron diffraction crystal structure.<sup>[132b]</sup>)

Not too many systems are known with strong and geometrically symmetric hydrogen bonds between different atom types. Even though the spectroscopic data predicts very short  $\text{N}-\text{H}\cdots\text{O}$  hydrogen bonds for a number of species,<sup>[126]</sup> the first example in a crystalline solid was characterized by neutron diffraction only very recently in the adduct of 4-methylpyridine and pentachlorophenol (Figure 26).<sup>[93]</sup> Even very small chemical changes in the system lead to loss of the symmetry, and to formation of either molecular  $\text{O}-\text{H}\cdots\text{N}$  or ionic  $\text{O}^-\cdots\text{H}-\text{N}^+$  hydrogen bonds.<sup>[133]</sup>

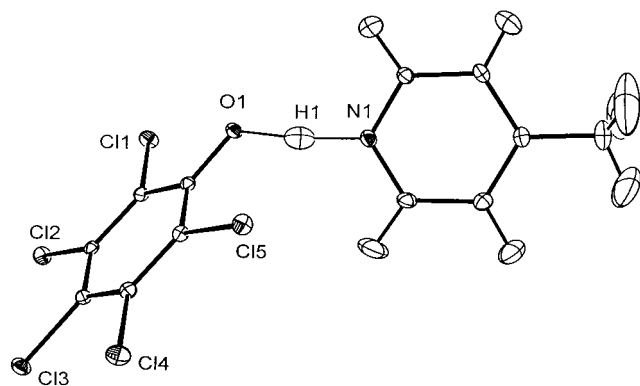


Figure 26. First example of an  $\text{O}-\text{H}\cdots\text{N}$  hydrogen bond with a centered position of the proton: pentachlorophenol/4-methylpyridine at 100 K characterized by neutron diffraction studies ( $\text{O}\cdots\text{N}=2.51$  Å).<sup>[93]</sup>

## 8. Weak and Less Common Hydrogen Bonds

In recent years, weak and less common types of hydrogen bonds have been a major topic in hydrogen bond research. Several reviews and a comprehensive book summarize this work,<sup>[8]</sup> and it is not necessary to review the field here once more in detail. The following remarks are intended to guide the interested reader through the large volume of modern literature on this topic.

Weak hydrogen bonds with  $\text{C}-\text{H}$  groups as donors are studied best. Formerly considered “unusual” or “nonconventional”, they are now discussed rather frequently in most fields of structural chemistry and biology. Dissociation energies are 0.4–4 kcal mol<sup>−1</sup>, with the majority < 2 kcal mol<sup>−1</sup>. At the low energy end of the range, the  $\text{C}-\text{H}\cdots\text{O}$  hydrogen bond gradually fades into a van der Waals interaction. The strong end of the interaction has not yet been well explored;  $\text{C}-\text{H}\cdots\text{A}$  bonds stronger than 4 kcal mol<sup>−1</sup> can readily be predicted to occur when very acidic  $\text{C}-\text{H}$  or very basic acceptor groups are involved. Many properties of  $\text{C}-\text{H}\cdots\text{O}/\text{N}/\text{Hal}$  interactions have been discussed in previous sections (Tables 1–3, Figures 2, 8, 23; Schemes 10, 19).  $\text{C}-\text{H}\cdots\text{O}$  hydrogen bonding in biological structures has also been investigated intensively.<sup>[134]</sup> Several recent reviews on the field are available.<sup>[81, 135–137]</sup>

A second type of weak hydrogen bond that has become well established in recent years are hydrogen bonds with  $\pi$  acceptors ( $\pi=\text{Ph}$ ,  $\text{C}\equiv\text{C}$ ,  $\text{C}=\text{C}$ ,  $\text{Py}$ ,  $\text{Im}$ , etc.; see Tables 1–3, Figure 10). The bond energies for strong  $\text{O}/\text{N}-\text{H}$  donors are higher than for  $\text{C}-\text{H}\cdots\text{A}$  bonds, about 2–4 kcal mol<sup>−1</sup> with neutral donors, and over 15 kcal mol<sup>−1</sup> with charged donors. In the latter case, the  $\text{X}-\text{H}\cdots\pi$  bond lies in the borderline region with the cation- $\pi$  interaction (see Section 2.6).  $\text{X}-\text{H}\cdots\pi$  hydrogen bonds occur in many fields of structural chemistry and biology, and there is a number of recent reviews that make a detailed discussion here unnecessary.<sup>[8, 27k, 138]</sup> A representative example is provided by an  $\text{N}-\text{H}\cdots\pi$  bond stabilizing a  $3_{10}$ -turn of a protein as shown in Figure 27.<sup>[80]</sup>

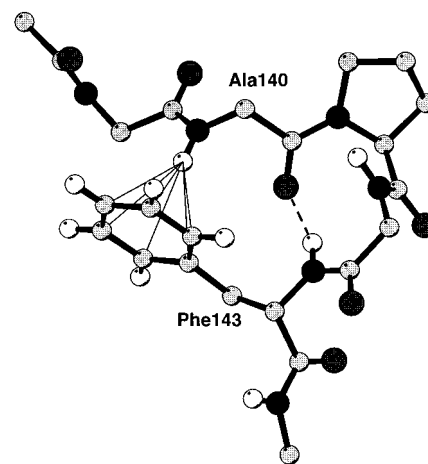


Figure 27. Example of an  $\text{N}-\text{H}\cdots\pi(\text{Ph})$  hydrogen bond in a protein (stabilizing a  $3_{10}$ -turn). Many related hydrogen bonds have been found that stabilize secondary structure elements.<sup>[80]</sup>

$\text{X}-\text{H}\cdots\pi$  interactions with weakly polar donors such as  $\text{C}-\text{H}$  groups are interesting because  $\text{C}-\text{H}$  groups span a wide range of polarities. With acidic donors such as  $\text{C}\equiv\text{C}-\text{H}$ , the  $\text{C}-\text{H}\cdots\pi$  interaction manifests itself through its spectroscopic properties as a “true” hydrogen bond,<sup>[139]</sup> and calculated energies are in the 2–3 kcal mol<sup>−1</sup> range (Table 1). A particularly interesting group is  $\text{C}\equiv\text{C}-\text{H}$ , because it can act as a donor and an acceptor simultaneously. This situation may lead to the formation of chains and rings,  $\text{C}\equiv\text{C}-\text{H}\cdots\text{C}\equiv\text{C}-\text{H}\cdots\text{C}\equiv\text{C}-\text{H}$  or  $\text{O}-\text{H}\cdots\text{C}\equiv\text{C}-\text{H}\cdots\text{O}-\text{H}$ , which are topologically

equivalent to hydrogen bond chains involving only O–H groups.<sup>[8, 50, 139, 140]</sup>

The C–H $\cdots\pi$  interaction keeps structure-determining ability as the C–H polarity decreases, but it becomes a matter of debate whether the term “hydrogen bond” is still adequate.<sup>[8]</sup> According to the definition proposed in Section 2.1, it is justified as long as some proton donor properties of C–H can be detected. Even if this definition is interpreted liberally, (Ph)C–H $\cdots$ Ph and –CH<sub>3</sub> $\cdots$ Ph interactions belong to the borderline region of hydrogen bonding. The phenomenon of the “CH/ $\pi$  interaction” in organic and biological chemistry has been explored and reviewed by Nishio et al. in a very interesting way.<sup>[141, 142]</sup> S–H groups have also been shown to donate hydrogen bonds to  $\pi$  acceptors, but bond energies seem to be very low (<1 kcal mol<sup>–1</sup>).<sup>[143]</sup>

Hydrogen bonds donated by metal hydrides, M–H $\cdots$ A, and accepted by electron-rich transition metal atoms, X–H $\cdots$ M, have been found in organometallic compounds.<sup>[8, 68, 144]</sup> The “dihydrogen bond” is formed between a protic X–H and a hydridic H–Y group, X $\delta^-$ –H $\delta^+$  $\cdots$ H $\delta^-$ –Y $\delta^+$ , such as between N–H and H–B.<sup>[145]</sup> Many other special kinds of hydrogen bonds have been documented structurally,<sup>[8]</sup> and investigated theoretically.<sup>[146]</sup> The role of organic fluorine as a hydrogen bond acceptor has attracted particular interest.<sup>[27q, 67, 147]</sup>

Finally, X–H groups with reverse polarity, X $\delta^+$ –H $\delta^-$ , need to be mentioned. They can form directional interactions X $\delta^+$ –H $\delta^-$  $\cdots$ A $\delta^+$  that are in many aspects analogous to a hydrogen bond. Since X–H does not act as proton donor, the term “hydrogen bond” as defined in Section 2.1 is not appropriate here. The alternative term “inverse hydrogen bond” suggested in a theoretical study reflects the chemical situation quite nicely.<sup>[148]</sup>

## 9. Bond Valence Concept

The idea that there is a more or less strict relationship between bond length and “bond order” or “valence”  $s$  dates back to Pauling.<sup>[3]</sup> Several expressions for  $s=f(d)$  have been proposed,<sup>[149, 150]</sup> but still the most popular one is Pauling’s exponential relationship [Eq. (1)], where  $d_0$  is the length of a

$$s = \exp[(d_0 - d)/b] \quad (1)$$

single bond with  $s=1$  and  $b$  is a constant (typically around 0.37 Å).<sup>[149]</sup> The rule of bond order conservation requires that the sum of bond orders ( $\Sigma s$ ) for each atom type is constant in all bonding situations (for example,  $\Sigma s=4$  for C,  $\Sigma s=2$  for O, etc.).

In a hydrogen bond X–H $\cdots$ A, there are two chemical bonds, X–H and H $\cdots$ A, and their bond orders must add up to 1, that is,  $s_{\text{XH}}+s_{\text{HA}}=1$ . Together with Equation (1), a relationship between the X–H and H $\cdots$ A bond lengths follows. For the homonuclear case, X=A, it is expressed by Equation (2):

$$r_{\text{XH}} = r_0 - b \ln[1 - \exp[(r_0 - r_{\text{HX}})/b]] \quad (2)$$

In multifurcated hydrogen bonds (Scheme 2) the bond orders of all H $\cdots$ A contacts must be included in the sum

$\Sigma s=1$ . The parameters  $r_0$  and  $b$  can be obtained by fitting Equation (2) to experimental structural data,<sup>[31a]</sup> such as those shown in Figure 14. The most recent values of  $r_0=0.928$  Å and  $b=0.393$ ,<sup>[36, 92]</sup> provide a good fit for O–H $\cdots$ O hydrogen bonds over the whole distance range (solid line in Figure 14a; there are slight but systematic deviations in the long distance range that could be remedied only by using a more sophisticated model function). Calculated bond orders  $s$  are given for O–H and H $\cdots$ O bonds over a wide distance range in Table 7. It may seem surprising that the valence of H $\cdots$ O in a hydrogen bond with  $d=1.8$  Å is as high as 0.11, whereas the one of O–H is reduced to as little as 0.89. This could be interpreted as a substantial covalent contribution even to moderate hydrogen bonds. The covalent contribution to the moderate hydrogen bonds in ice has recently been studied by Compton scattering methods.<sup>[151]</sup>

Table 7. Bond orders of O–H and H $\cdots$ O bonds as calculated from Equation (1) using the parameters  $r_{0,\text{OH}}=0.927$  Å,  $b_{\text{OH}}=0.395$  Å.<sup>[92]</sup>

| O–H  | $s$  | H $\cdots$ O | $s$  |
|------|------|--------------|------|
| 0.97 | 0.90 | 1.20         | 0.50 |
| 0.98 | 0.87 | 1.30         | 0.39 |
| 0.99 | 0.85 | 1.40         | 0.30 |
| 1.0  | 0.83 | 1.50         | 0.23 |
| 1.02 | 0.79 | 1.60         | 0.18 |
| 1.04 | 0.75 | 1.70         | 0.14 |
| 1.06 | 0.71 | 1.80         | 0.11 |
| 1.08 | 0.69 | 1.90         | 0.08 |
| 1.10 | 0.65 | 2.00         | 0.07 |
| 1.15 | 0.57 | 2.20         | 0.04 |
| 1.20 | 0.50 | 2.40         | 0.02 |

Much less experimental material is available for N–H $\cdots$ N hydrogen bonds. In particular, the central region of the plot corresponding to Figure 14a is completely devoid of data points. The parameters  $r_{0,\text{NH}}=0.996$  Å and  $b_{\text{NH}}=0.381$  are much less reliable, and should not be expected to represent the region of very short hydrogen bonds very accurately.<sup>[94]</sup> The parameters for heteronuclear hydrogen bonds are also of limited accuracy because of small numbers of data.<sup>[36]</sup>

The bond valence concept can be used to rationalize effects of hydrogen bonding on non-hydrogen molecular frameworks, and reasonable numerical estimates can often be obtained. For example, the rule of bond order conservation requires that the O=C bond in C–O–H $\cdots$ O=C is weakened by the amount  $s_{\text{HO}}$ , and is lengthened correspondingly.<sup>[152]</sup>

For covalent bonds, it has been shown that  $s$  is proportional to the electron density at the bond critical point,  $\rho_{\text{BCP}}$ .<sup>[39a]</sup> In O–H $\cdots$ O hydrogen bonds, both  $\rho_{\text{BCP}}$  and  $s$  depend in an exponential way on the H $\cdots$ O distance [Figure 3 and Equation (1), respectively], which implies the relationship  $s \sim \rho_{\text{BCP}}$ , at least approximately.

## 10. Summary and Outlook

The present article has given an overview of hydrogen bonding in the solid state, with a focus on the structural properties. It is the mere volume of the published literature

that requires this article to concentrate on the fundamentals of the structural aspects. It was shown that the hydrogen bond phenomenon is a very broad one: there are dozens of different  $X-H \cdots A$  interactions that occur commonly in the condensed phases, and in addition there are innumerable less common ones. Dissociation energies span more than two orders of magnitude, about  $0.2-40 \text{ kcal mol}^{-1}$ . Within this range, the nature of the interaction is not constant, but includes electrostatic, covalent, and dispersion contributions in varying weights. To further increase the complexity, the hydrogen bond has broad transition regions—"grey areas"—with the covalent bond, the van der Waals interaction, the ionic interaction, and also the cation- $\pi$  interaction.

Looking into the future of a complex subject is always difficult, but a little history sometimes helps. The field of hydrogen bonds did not evolve smoothly, but saw periods of rapid development and periods of stagnation. In particular in the 1980s, many researchers felt that the field was more or less closed. Around 1990, the field opened again, and it is still moving rapidly. The present boom is related to the broad spectrum of fields that are involved: material science, inorganic and organic chemistry, biology, and pharmacy. In none of these areas has the role and function of hydrogen bonds been explored satisfactorily, nor has hydrogen bond research reached a level that allows the interaction to be *controlled* (with the exception of some aspects of "crystal engineering"). With this background, it is not too daring to predict that gaining control of hydrogen bonds, and developing corresponding tools to be utilized in the fields mentioned above will be the next goal.

*I would like to thank the many co-authors of my original publications who have helped me gain insight into the fascinating topic of hydrogen bonding. There are too many names to be mentioned, over 50 in total, so I may only name a few individually: G. R. Desiraju, G. Koellner, J. Kroon, W. Saenger, and J. L. Sussman. Over the years, various sources have provided financial support, and I would like to thank in particular the Deutsche Forschungsgemeinschaft and the Minerva Foundation. A referee of this review has provided an extraordinary number of helpful suggestions for improvement. I would like to thank this anonymous colleague for the very careful reading and the large amount of time spent.*

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- [1] The discovery of the hydrogen bond cannot be attributed to a single author, and no genuine "first paper" can be quoted. Specialized articles developing relevant ideas began to appear at the beginning of the 20th century, mainly in the German and English literature, but the far-reaching relevance of the hydrogen bond was not yet recognized. More elaborate studies and clear general concepts were published from the 1920s on, with pioneering roles usually attributed to Latimer and Rodebush, Huggins, and Pauling. By the end of the 1930s, a "classical" view of the hydrogen bond was established that dominated the field for half a century. Research into hydrogen bonds experienced a peak in the 1950s and 1960s, followed by relative stagnation from the mid-1970s to the late 1980s. An intense revival occurred from about 1990 on. Theoretical concepts were long dominated by Coulsons partitioning into resonance forms, which were later replaced by modern quantum chemical models. Historical surveys can be found in the books cited below.<sup>[2-9]</sup>

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- molecules, are quite “strong” for one researcher and fairly “weak” for the other one, depending on the personal focus of interest. In a general view on hydrogen bonds, and essentially following the categorization of Jeffrey,<sup>[6]</sup> it seems appropriate to attach the names “strong” and “weak” to the extremes of the scale, and use a term such as “moderate” for the intermediate range. One might note that chemically, the difference between “strong” (quasi-covalent nature) and “moderate” (mainly electrostatic) is larger than between “moderate” (electrostatic) and “weak” (electrostatic/dispersion).
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# High-Pressure Syntheses of Novel Binary Nitrogen Compounds of Main Group Elements\*\*

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*In memoriam Holger Behrends (1975–2000)*

The application of high-pressure methods in the search for novel materials usually requires additional effort compared to syntheses at ambient pressure. Depending on the desired  $p/T$  conditions different methods may be used. Special techniques and experimental apparatus such as shock waves, diamond anvil cells, and multianvil presses, which have been applied mainly by earth scientists and physicists in the past, are increasingly being applied by synthetic chemists and material scientists. A series of fascinating discoveries have been made recently as is demonstrated by three examples of binary nitrogen compounds: 1) Diazenides, compounds with  $N_2^{2-}$  ions, were obtained as single-phase products and structurally characterized for the first time. 2) At 11 GPa and 1800 K a phosphorus(v) nitride was prepared, which contains tetragonal  $PN_5$  pyramids as a novel structural motif. 3) Macroscopic amounts of spinel silicon nitride were synthesized by shock-wave techniques, which allows the comprehensive characterization and possibly the implementation of this new hard material.

## 1. Introduction

Temperature, reaction time, and concentration or reactant ratios are without question the most widely used parameters in preparative chemistry. Another very crucial parameter for the successful performance and optimization of chemical reactions is the pressure, which is less frequently used. The major reason for this is certainly the additional experimental effort required for applying high-pressure methods.<sup>[1]</sup> The “standard high-pressure technique” in the field of synthetic chemistry is based on the application of autoclaves and high-pressure bombs. In recent years the application of these techniques was further expanded, for example for reactions in supercritical media.<sup>[2]</sup> Methods for the generation of extremely high pressures ( $p > 1$  GPa) have been developed in the fields of earth sciences. Currently, these techniques are increasingly used in preparative inorganic chemistry and material science, which is reflected by several recently published review articles.<sup>[3]</sup>

Table 1 shows a comparison of the presently most frequently used high-pressure techniques. Each of these methods represents a compromise with respect to maximum pressure, temperature, sample size, costs, and experimental effort. Autoclaves and high-pressure bombs are easy to operate, cheap, and allow the production of large samples; however, the  $p/T$  range is rather limited. “Large” presses such as belt or multianvil equipment (Figure 1) are much more expensive and more difficult to operate;<sup>[1c,d]</sup> however, they allow pressures and temperatures up to 25 GPa and 3000 K, respectively, and produce amounts of sample that permits convenient characterization with the common analytical techniques. Even higher pressures and temperatures are achievable with laser-heated diamond anvil cells (Figure 2).<sup>[1e,f]</sup> Owing to the transparency of the diamond anvils they offer the opportunity of in situ examinations, for example by vibrational spectroscopy or X-ray diffraction. Disadvantages are the small sample sizes ( $\ll 1$  mg). Consequently, energy-dispersive X-ray analysis (EDX) and electron energy loss spectroscopy (EELS) measurements in transmission electron microscopes are usually necessary to estimate the elemental composition of the products.

Shock-wave syntheses methods<sup>[1g,h]</sup> can be subdivided in three classes: 1) “flyer-plate” or “impact” methods, in which a projectile (flyer) is shot onto an especially prepared (mixture)

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Table 1. Overview of high-pressure techniques and apparatus currently used in preparative chemistry.

|                   | Autoclaves/Pressure bombs   | "Piston–cylinder-presses" | "Large" presses <sup>[a]</sup> | Shock syntheses <sup>[b]</sup> | Diamond anvil cells           |
|-------------------|-----------------------------|---------------------------|--------------------------------|--------------------------------|-------------------------------|
| $p_{\max}$ [GPa]  | 1.5                         | 5                         | 25 (40 <sup>[c]</sup> )        | 150 <sup>[d]</sup>             | 500                           |
| $T_{\max}$ [K]    | 1200 (2000 <sup>[e]</sup> ) | 2000                      | 3000                           | 5000                           | 7000                          |
| sample size       | 1 kg (10 g) <sup>[f]</sup>  | < 10 g <sup>[f,g]</sup>   | 0.001–1 g <sup>[g]</sup>       | 0.1–500 g <sup>[h]</sup>       | ≪ 1 mg                        |
| prime costs [€]   | 500–25 000                  | 2500–75 000               | 50 000–400 000                 | > 25 000 <sup>[i]</sup>        | 75 000–150 000 <sup>[j]</sup> |
| cost of operation | low                         | low–moderate              | high                           | moderate–very high             | low–moderate                  |

[a] For example, multianvil presses. [b] For example, flyer plate or detonative syntheses. [c] Using diamond-based materials for the anvils. [d] By "impact" experiments much higher pressures may be generated, but usually it is very difficult to recover the sample. [e] Using IHPV ("internally heated pressure vessels"). [f] Depending on the pressure range different types of devices are used. [g] Sample sizes strongly depend on the desired pressure range. [h] For very large samples (> 10 g), costs increase disproportionately, so that it is better to perform several experiments one after the other. [i] Strongly dependent on sample size and applied technique. [j] Including CO<sub>2</sub> or YAG laser for heating as well as equipment for in situ temperature and in situ pressure determination (Rubin-fluorescences).

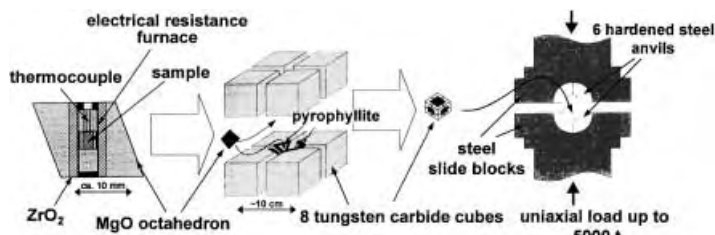


Figure 1. Schematic sketch of a diamond anvil cell.

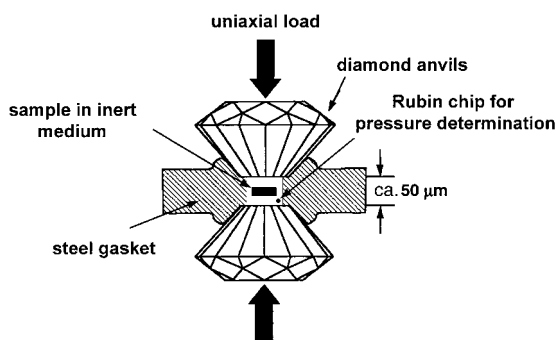


Figure 2. Schematic sketch of a two-stage cubic octahedral multianvil press.

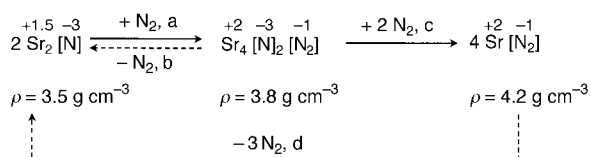
of starting materials, 2) shock compressions or compactions, which usually are based on an explosive charge, which is in direct contact with the starting materials to be densified, producing a pressure wave, and 3) detonative syntheses, in which a precursor–explosive–mixture is ignited in a suitable vessel. All three techniques offer the opportunity to produce larger amounts of products. The disadvantages of shock-wave methods are obvious: The desired  $p/T$  condition can only be perpetuated for a short time (ca. 1 μs). Other frequently applied equipment, such as Bridgman or belt presses, was often modified and adapted to special requirements. Furthermore, there are other rarely used approaches such as the volume decrease upon solidification of melts. For all static high-pressure techniques the maximum pressure decreases with increasing temperature (strength decline) and increases with smaller sample sizes.

Similar to the field of oxides more and more research over the last few years has been concerned with ternary, quaternary and multinary nitrogen compounds.<sup>[4]</sup> That the application of high pressure provides access to new interesting binary phases today is evidenced in the following by examples of novel nitrogen compounds of the main group elements.

## 2. High-Pressure Synthesis and Structural Characterization of Diazenides

Ionic oxygen compounds such as oxides ( $O^{2-}$ ), ozonides ( $O_3^-$ ), peroxides ( $O_2^{2-}$ ), and hyper- or superoxides ( $O_2^-$ ) are well known;<sup>[5]</sup> a comparison with nitride compounds raises the question, whether there are, in addition to nitride and azide ions, other anionic species—for example "pernitride" ions ( $N_2^{2-}$ )—that are stable in the condensed phase. There are numerous metal complexes known, in which the  $N_2$  ligands may be considered as  $N_2^{2-}$  or  $N_2^{4-}$  ions.<sup>[6]</sup> This is particularly true for complexes of the early transition metals, which contain  $\mu-\eta^1:\eta^1$ -bridging  $N_2$  molecules. Furthermore,  $N_2^{2-}$  ions generated by ion implantation in CdS were detected by ESR spectroscopy.<sup>[7]</sup> The high-pressure synthesis of  $BaN_2$  was reported in 1953.<sup>[8]</sup> Saltlike pernitrides of the alkaline earth metals containing the  $N_2^{4-}$  ion have also been mentioned in literature.<sup>[9]</sup> The existence of these compounds was supported by elemental analyses, IR spectra, as well as by the detection of hydrazine in the hydrolysis products.<sup>[9]</sup> However, a structure determination of a compound with  $N_2^{x-}$  ions has not been accomplished yet.

Moreover, the number of binary nitrogen compounds of alkali metals and alkaline earth metals is still relatively small.<sup>[10]</sup> For the Sr/N system,  $Sr_3N_2$ ,  $Sr_8N_5$ , and  $SrN$  have been reported,<sup>[10a]</sup> but only the subnitride  $Sr_2N$ <sup>[10b,c]</sup> and the azide  $Sr(N_3)_2$ <sup>[10d]</sup> have been structurally characterized. Against this background, the high-pressure synthesis and structural characterization of "diazenides"  $SrN$  and  $SrN_2$ , that is compounds with  $N_2^{2-}$  ions, by Kniep et al.<sup>[11]</sup> is particularly remarkable (Scheme 1). Phase-pure  $SrN$  was synthesized starting from  $Sr_2N$  at 920 K, 0.04 GPa, and a reaction time of 72 h. Increasing the pressure to 0.55 GPa under otherwise similar conditions furnished  $SrN_2$ . The synthesis was carried out in a special autoclave, in which the initial  $N_2$  pressure was 0.02 and 0.275 GPa, respectively.



Scheme 1. Synthesis and decomposition of the strontium diazenides  $SrN$  and  $SrN_2$ : a) 920 K, 0.04 GPa, 3 d; b) 573–673 K, 100 kPa; c) 920 K, 0.55 GPa, 3 d; d) 618–673 K, 100 kPa.

The structures of SrN and SrN<sub>2</sub>, which are metastable at 20 °C and 100 kPa, were determined by X-ray and neutron diffraction using powders. SrN<sub>2</sub> crystallizes isotypically to the corresponding alkaline earth acetylides in a tetragonal distorted NaCl structure (Figure 3, left). SrN is described as a nitride-diazene: (Sr<sup>2+</sup>)<sub>4</sub>[N<sup>3-</sup>]<sub>2</sub>[N<sub>2</sub><sup>2-</sup>]. The structure can be derived from Sr<sub>2</sub>N (inverse CdCl<sub>2</sub> type) by adding N<sub>2</sub><sup>2-</sup> ions into the octahedral sites between the Sr<sub>2</sub>N layers. The N–N distance within the diazenide ions (ca. 122.5 pm) corresponds well with that in  $\mu\text{-}\eta^1\text{-}\eta^1\text{-N}_2$  complexes, which may be considered to contain M-(N<sub>2</sub><sup>2-</sup>)-M units.<sup>[6]</sup> The N–N distances in organic *cis*- (124.5 pm) and *trans*-dialkyl diazo compounds (122.2 pm) as well as the O–O distance in the oxygen molecule (120.7 pm) are also in the same region.<sup>[12]</sup> Ab initio calculations for singlet-N<sub>2</sub><sup>2-</sup> ions gave a value of 123.8 pm, which is also very close to the results found for the solid-state structures.<sup>[13]</sup>

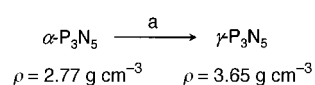
Simon and Kniep et al. have also reported the synthesis of barium pernitride, BaN<sub>2</sub>,<sup>[14]</sup> which was obtained from the elements at 0.56 GPa and 920 K or by careful thermal decomposition of dry barium azide Ba(N<sub>3</sub>)<sub>2</sub> at 100–300 kPa and 470–530 K. The crystal structure of BaN<sub>2</sub> was again determined by powder X-ray and neutron diffraction. In contrast to the structure of SrN<sub>2</sub> which contains N<sub>2</sub> dumbbells oriented along the *c* axis and which crystallizes in the space group *I4/mmm*, the diffraction data for BaN<sub>2</sub> was more successfully refined in the space group *C2/c*. Here the octahedrally coordinated N<sub>2</sub> units are arranged perpendicular to the *c* axis and alternating by 90°. The N–N distance is almost identical to that for SrN<sub>2</sub>. Interestingly, measurements of the magnetic susceptibility indicate that the substance is metallic, which, according to simulations of the band structure, is attributed to Ba(5d)-N(2p) interactions.

### 3. Synthesis of $\gamma\text{-P}_3\text{N}_5$ in a Multianvil Press: A Compound with Tetragonal PN<sub>5</sub> Pyramids

In contrast to the diazenides P/N phases should be interpreted as covalent inorganic polymers. They are similar to B/N and Si/N compounds in that they form tetrahedral EN<sub>4</sub> units, which can be linked to give oligomeric and polymeric

networks.<sup>[15]</sup> Unlike for boron nitrides (*h*- and *c*-BN) and silicon nitrides ( $\alpha$ - and  $\beta$ -Si<sub>3</sub>N<sub>4</sub>), the structure determination of the phosphorus nitrides PN and P<sub>3</sub>N<sub>5</sub> turned out to be more difficult.<sup>[16]</sup> Thus the structure of  $\alpha$ -P<sub>3</sub>N<sub>5</sub> was first resolved in 1997 by using powder diffraction with synchrotron radiation, after a synthesis route to phase-pure samples had been developed.<sup>[17]</sup> This solid crystallizes in a novel structure type consisting of a three-dimensional network of corner- and edge-sharing PN<sub>4</sub> tetrahedra. Two fifths of the N atoms are threefold and three fifths are twofold coordinated with P atoms. The crystal structures of amorphous PN and  $\beta$ -P<sub>3</sub>N<sub>5</sub> (according to high-resolution transmission electron microscopy (HRTEM) studies an ordered stacking variant of  $\alpha$ -P<sub>3</sub>N<sub>5</sub>) are not known in detail.<sup>[15–17]</sup>

Recently, a novel high-pressure phase of phosphorus(v) nitride  $\gamma$ -P<sub>3</sub>N<sub>5</sub> was synthesized at 11 GPa and *T* = 1800 K using the multianvil technique (Figure 1; Scheme 2).<sup>[18]</sup> The



Scheme 2. Synthesis of  $\gamma$ -P<sub>3</sub>N<sub>5</sub> in a multianvil press: a) 1773 K, 11 GPa, 5 min.

compound consists of one third PN<sub>4</sub> tetrahedra and two thirds tetragonal PN<sub>5</sub> pyramids. In contrast to the  $\alpha$ -phase a larger fraction of the N atoms (i.e. four fifths) are threefold coordinated with phosphorus and only one fifth is bonded to two P atoms. Thus, starting from a  $^3[\text{P}_3^{[4]}\text{N}_3^{[2]}\text{N}_2^{[3]}]$  network a  $^{\infty}[\text{P}_2^{[4]}\text{P}_2^{[5]}\text{N}_2^{[2]}\text{N}_4^{[3]}]$  structure was formed (Figure 3, center). The three-coordinate N atoms are sp<sup>2</sup>-hybridized in both phases (sum of bond angles ca. 360°), while the P–N<sup>[2]</sup>–P angle of 142–171° in  $\alpha$ -P<sub>3</sub>N<sub>5</sub> decreases to 111° in  $\gamma$ -P<sub>3</sub>N<sub>5</sub>.

The most remarkable feature of the P<sub>3</sub>N<sub>5</sub> high-pressure phase is the novel PN<sub>x</sub> coordination geometry. Although distorted trigonal PN<sub>5</sub> bipyramids have been found in molecular compounds, square or tetragonal PN<sub>5</sub> pyramids were not known previously.<sup>[18]</sup> Combined with the increase of the mean coordination numbers, an increase of the average bond length is expected due to the pressure–distance rule; besides, a 32 % decrease of the volume is observed. A similar increase of the coordination number combined with a

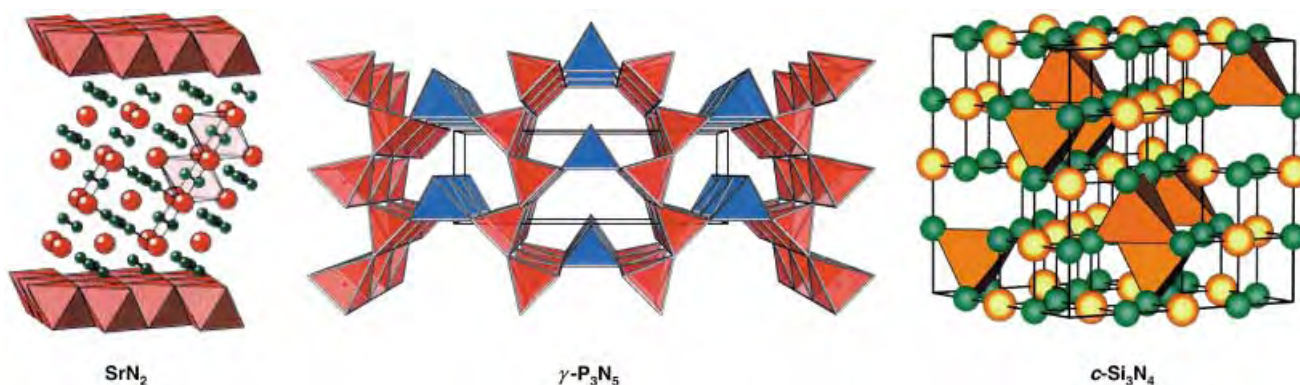


Figure 3. Left: Crystal structure of SrN<sub>2</sub>,<sup>[11]</sup> the layers at the top and bottom edges represent (N<sub>2</sub>)Sr<sub>6/3</sub> octahedra, while a ball-and-stick-illustration is used in between; red: Sr<sup>2+</sup>, green N<sub>2</sub><sup>2-</sup>. Center: Polyhedral representation of the three-dimensional network structure of  $\gamma$ -P<sub>3</sub>N<sub>5</sub>; <sup>[18]</sup> red: PN<sub>5</sub> pyramids, blue: PN<sub>4</sub> tetrahedra; right: Si<sub>3</sub>N<sub>4</sub> spinel structure<sup>[24a, b]</sup>; green: N; yellow: octahedrally coordinated Si; orange: SiN<sub>4</sub> tetrahedra.

corresponding volume decrease was found for the recently discovered high-pressure phase of  $\text{Si}_3\text{N}_4$  (see Section 4). From an initial  $\infty[\text{Si}_3^{[4]}\text{N}_4^{[3]}]$  network a  $\infty[\text{Si}_2^{[6]}\text{Si}^{[4]}\text{N}_4^{[4]}]$  structure was formed at 12 GPa and 1600 K.

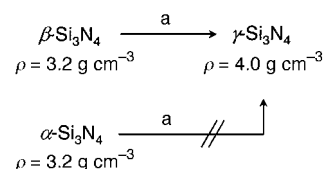
The high-pressure phases of  $\text{Si}_3\text{N}_4$  and  $\text{P}_3\text{N}_5$  are potential materials for engineering ceramics due to their temperature resistance, hardness, and chemical inertness. This statement is most likely also valid for related ternary and multinary nitride high-pressure phases such as spinel-SiAlONs<sup>[19]</sup> as well as for nitridophosphates<sup>[20]</sup> and possibly also for nitridosilicates and nitridoborates.

#### 4. Spinel- $\text{Si}_3\text{N}_4$ Synthesized by Shock-Wave Methods

Until 1999 there were six binary  $\text{EN}_x$  phases of the heavy elements of the fourth main group known:  $\alpha$ - and  $\beta$ - $\text{Si}_3\text{N}_4$ ,  $\alpha$ - and  $\beta$ - $\text{Ge}_3\text{N}_4$  as well as  $\alpha$ - and  $\beta$ - $\text{Pb}(\text{N}_3)_2$ . Additionally, certain subnitrides have been reported, which, however, are frequently amorphous and structurally not well characterized, but nevertheless are partly used as functional materials.<sup>[21]</sup> In addition, there are numerous molecular  $\text{CN}_x$  compounds known.<sup>[22]</sup> However, the existence of a hard material with the molecular formula  $\text{C}_3\text{N}_4$ , that is a carbon(iv) nitride, has not been confirmed despite several reports about its successful synthesis.<sup>[23]</sup>

In 1999 three novel spinel nitride phases of the elements Si, Ge, and Sn were discovered almost simultaneously.<sup>[24]</sup> Whereas  $c$ - $\text{Si}_3\text{N}_4$  ( $\gamma$ - $\text{Si}_3\text{N}_4$ , see Figure 3, right)<sup>[24a,b]</sup> as well as  $c$ - $\text{Ge}_3\text{N}_4$  ( $\gamma$ - $\text{Ge}_3\text{N}_4$ )<sup>[24c,d]</sup> were synthesized in diamond anvil cells and multianvil presses at  $p \geq 12$  GPa, the preparation of  $\text{Sn}_3\text{N}_4$ <sup>[24e]</sup>—the first binary Sn/N-compound—was accomplished at ambient pressure. Owing to the importance<sup>[25]</sup> of  $\beta$ -silicon nitride as a ceramic material for cutting tools, machine and engine components, as well as electronic parts, the discovery of another  $\text{Si}_3\text{N}_4$  modification attracted much interest.<sup>[26]</sup> The increase in density ( $4.0 \text{ g cm}^{-3}$ ) by about 25% compared to the formerly known modifications ( $3.2 \text{ g cm}^{-3}$ ) and a bulk modulus of about 310 GPa might indicate an application of the cubic  $\text{Si}_3\text{N}_4$  phase as a hard material. Syntheses on a larger scale than possible in diamond-anvil cells or multianvil presses are required for further characterization of the materials properties and possibly the fabrication of  $c$ - $\text{Si}_3\text{N}_4$ -based components for practical utilization. Currently, the equipment used in industry for the commercial preparation of diamond and  $c$ -BN is limited to a maximum pressure of 6 GPa,<sup>[27]</sup> which is not sufficient for the synthesis of  $c$ - $\text{Si}_3\text{N}_4$ . An alternative to static high-pressure techniques are dynamic methods, which have been used successfully to produce the ultra-hard materials  $c$ -BN and diamond.<sup>[1g,h]</sup>

Already shortly after the discovery of spinel silicon nitride Sekine et al. obtained  $c$ - $\text{Si}_3\text{N}_4$  in high yields by shock-wave methods (Scheme 3).<sup>[28]</sup> Submicrometer powders of pure  $\beta$ - $\text{Si}_3\text{N}_4$  or a  $\alpha$ -/ $\beta$ - $\text{Si}_3\text{N}_4$  mixture were blended with copper. Targets wrapped in copper or platinum hulls were cannonaded with steel or platinum projectiles.<sup>[28a]</sup> By varying the projectile velocity between 1.5 and 2.1  $\text{km s}^{-1}$  pressures of 12 to 115 GPa and temperatures above 3000 K were generated



Scheme 3. Synthesis of  $\gamma$ - $\text{Si}_3\text{N}_4$  from  $\beta$ - $\text{Si}_3\text{N}_4$  by shock-wave methods: a) 3000 K, 50 GPa, 1  $\mu\text{s}$ . The formation from  $\alpha$ - $\text{Si}_3\text{N}_4$  under the same conditions is not successful.

for about one microsecond. The products were characterized after the removal of the copper with  $\text{HNO}_3$  by X-ray structure analysis, transmission electron microscopy, and EDX. A maximum  $c$ - $\text{Si}_3\text{N}_4$  yield of 80% (!) was obtained at 50 GPa and 2400 K (decomposition of the silicon nitride was observed at still higher pressures and temperatures). The particle size of the  $c$ - $\text{Si}_3\text{N}_4$  lay between 10 and 50 nm. Interestingly,  $\alpha$ - $\text{Si}_3\text{N}_4$  does not transform into the spinel phase under the same conditions. This indicates a diffusionless (martensitic) transformation from  $\beta$ - to  $c$ - $\text{Si}_3\text{N}_4$ .

In another report from the research group of Sekine<sup>[28b]</sup> sintered dense  $\beta$ - $\text{Si}_3\text{N}_4$  discs ( $1 \times 1.2 \times 0.3 \text{ cm}$ ) were cannonaded with polycarbonate, steel, and tungsten projectiles. The minimum pressure of 36 GPa required to produce  $c$ - $\text{Si}_3\text{N}_4$  in these experiments is much higher than that for the static experiments, which is attributed to the low temperature of 460 K. A complete transformation into the high-pressure phase was not observed even at the highest pressure of 150 GPa generated in the experiments, but a 100% conversion was extrapolated for  $p_{\text{max}} = 180$  GPa. However, according to recent calculations for this pressure range, a further high-pressure modification should be formed, which is similar to the  $\text{CaTi}_2\text{O}_4$  structure, and contains  $\text{SiN}_6$  prisms as well as  $\text{SiN}_6$  octahedra.<sup>[29]</sup> Recently published diamond anvil cell studies indicate that at 34 GPa/RT a further new  $\text{Si}_3\text{N}_4$  phase already forms:  $\delta$ - $\text{Si}_3\text{N}_4$ .<sup>[30]</sup> However, the structure of this compound has not been solved so far.

A thorough design and analysis of the impact experiments allowed a determination of the pressure/density function (Hugoniot) for  $\text{Si}_3\text{N}_4$ . Using these data and the Birch–Murnaghan equation of state a value of  $300 \pm 10$  GPa was estimated for the bulk compression modulus. This result corresponds well with the results of theoretical predictions<sup>[24a]</sup> as well as recent static measurements of the compressibility of  $c$ - $\text{Si}_3\text{N}_4$  in a diamond anvil cell.<sup>[31]</sup>

#### 5. Conclusions

It is clear since the development of the ammonia synthesis and the preparation of  $c$ -BN that the application of high pressure is very useful for obtaining  $\text{EN}_x$  compounds and materials. Interesting new solids are still being synthesized by high-pressure techniques today: Kniep et al. succeeded in confirming that besides the three formerly known homopolyatomic nitrogen species  $\text{N}_2$ ,  $\text{N}_3^-$ , and  $\text{N}_5^+$  also  $\text{N}_2^{2-}$  ions are stable in the solid phase.<sup>[11]</sup> Schnick et al. demonstrated that in addition to  $\text{PN}_4$  tetrahedra also tetragonal  $\text{PN}_5$  pyramids occur as structural motifs in P–N-compounds.<sup>[18]</sup> Sekine et al. have shown that dynamic techniques may be used to produce

and characterize compounds, which are available only in very small amounts with static techniques.<sup>[28]</sup>

Another group of  $\text{EN}_x$  high-pressure phases of main group elements are the nitrides  $\text{AlN}$ ,  $\text{GaN}$ , and  $\text{InN}$  with rock salt structure.<sup>[32]</sup> These phases are noteworthy given the enormous interest in the corresponding Wurtzite phases for semiconductor research, and it is surprising that very little has been reported on these materials to date.<sup>[32]</sup>

Of course, the fascinating results that have been obtained recently by high-pressure techniques are not limited to binary nitrogen compounds of main group elements. For example, the discovery of a diamondlike  $\text{BC}_2\text{N}$  phase, which—shortly after the structural analysis of a graphite  $\text{BC}_2\text{N}$  modification obtained at 3–5 GPa<sup>[33]</sup>—was prepared in a multianvil press at 18 GPa and 2200 K, is a milestone in hard materials research.<sup>[34]</sup> This first cubic B/C/N phase now represents the second hardest substance after diamond.

Even for “simple” compounds such as elemental nitrogen, elemental carbon in the form of fullerenes, or carbon dioxide, highly interesting results were obtained upon compression in diamond anvil cells. At a pressure of 140 GPa polymeric  $\text{N}_2$  was formed. The product is stable at ambient pressure up to a temperature of 100 K.<sup>[35]</sup> In a similar manner  $\text{CO}_2$  was transformed at >35 GPa and 1800 K into a solid with a tridymite-like  $\text{SiO}_2$  structure, which is detectable at room temperature up to a pressure of 1 GPa.<sup>[36]</sup> Depending on the  $p/T$  conditions, fullerenes are polymerized to give one-, two-, and three-dimensional (sometimes crystalline) networks,<sup>[37]</sup> which are characterized, for example, by very interesting magnetic properties.<sup>[38]</sup>

The examples presented here show how useful the application of high pressure is for preparative chemistry, and that the additional costs and effort can be worthwhile. Further propagation and application of high-pressure techniques will certainly produce interesting and useful materials in the future.

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# Molecular Gastronomy

Hervé This\*

## 1. Culinary Proverbs and Know-How

Molecular Gastronomy? This name seems unnecessarily pompous. If the discipline is only the chemical and physical exploration of culinary processes, why did we give a new name to what seems only food science? A look at the history of science below will show it.

Our discipline is born from observations that we made in the 1980s with the physicist Nicholas Kurti (1908–1998, former professor of physics in Oxford, FRS):<sup>[1]</sup> at home or in the restaurants of industrialized or developing countries, culinary activity is based on empirical traditions and not on the rational understanding of the phenomena involved in the culinary processes. This is the reason why culinary books (even modern ones) are a strange mixture of remarkable (sometimes very precise) observations and dubious, or false advice.

It is written, for example, that suckling pigs must have the head cut as soon as they are outside the oven, otherwise the crackling of the skin is lost; is it true?<sup>[2]</sup> It is said (in France) that women should not make mayonnaise<sup>[3]</sup> on “certain days of the month” (i.e. when they have their periods), otherwise the sauce fails; is it true? Anyway this idea does not hold in England; there, instead, it is said that women should not rub meat with salt on these particular days.<sup>[4]</sup> It is written that the potato slices in a potato salad are more tender if the slices are put in the dressing when they are still hot; is it true?<sup>[5]</sup> The cooks—and even certain chemists—write that, when preparing a stock, the meat should be put into cold water, otherwise “albumin coagulation” makes a crust at the surface of the meat and prevents juice losses into the water; the stock would have less taste. Is this true, as stock preparation takes as long as six hours?<sup>[6]</sup>

Up to now, we have collected more than one thousand open questions of this kind.<sup>[7]</sup> Their rational study obviously needs a multidisciplinary approach: culinary tests should be followed by interpretations of observed phenomena based on chemistry, and also physics, biology, history, and sociology. The

exploration of what we call culinary proverbs, know-how, or old-wives tales is the core of molecular gastronomy.

This discipline is clearly part of food science, which has been providing food to populations for centuries. But it is a specific part, as it focuses primarily on domestic or restaurant cooking, and not on food in general. We decided to make molecular gastronomy a particular discipline, because we realized that there was a growing gap between food science and home cooking.

In the 17th or 18th centuries, this distinction could not have been made because the pioneers of food science were indeed interested in cooking: Antoine Laurent de Lavoisier (1743–1794) wanted to explore culinary processes when he measured the density of stocks,<sup>[8]</sup> Antoine Augustin Parmentier (1737–1813) proposed culinary processes as he tried to introduce potatoes in home cooking,<sup>[9]</sup> Justus von Liebig (1803–1873) and others wanted to rationalize stock preparation,<sup>[6]</sup> Eugène Chevreul (1786–1889) obtained major results in chemistry when he explored the chemical properties of fats.

“Classical” food science was (and still is, of course) very useful as, thanks to close collaboration with the food industry, it succeeded in giving enough to eat to western populations. But it slowly became more concerned with food and industrial food transformations than in domestic cooking. And as home economy is no longer taught in the schools of many countries, daily food preparation by millions of individuals is based only on recipes published in culinary books. These books, written by amateurs or professionals, but generally not by scientists, contain a lot of truths but also a lot of mistakes.

For example, it is true that a steak cooked in a pan turns brown. However, it is not true that, as said by many cooks, this browning is due to caramelization; chemists know that the browning is due to Maillard reaction, between amino acids and carbohydrates (see Figure 1),<sup>[10]</sup> and to many other reactions: just think of all the reactive groups in food molecules, and all the reaction possibilities!

It is also true that a thick sauce is formed when oil is slowly added to egg yolk while whisking. However, it is not true, as some cooks think, that the oil and the yolk mix perfectly; chemists know that the oil is divided into droplets (diameter between 0.01 to 0.1 mm), surrounded by denatured proteins and phospholipids (present in the yolk), that are packed into the small quantity of water that comes from the yolk (about 50 % of the yolk).<sup>[11]</sup>

Clearly culinary activity would improve greatly if we dropped the bad and kept the good. The development of

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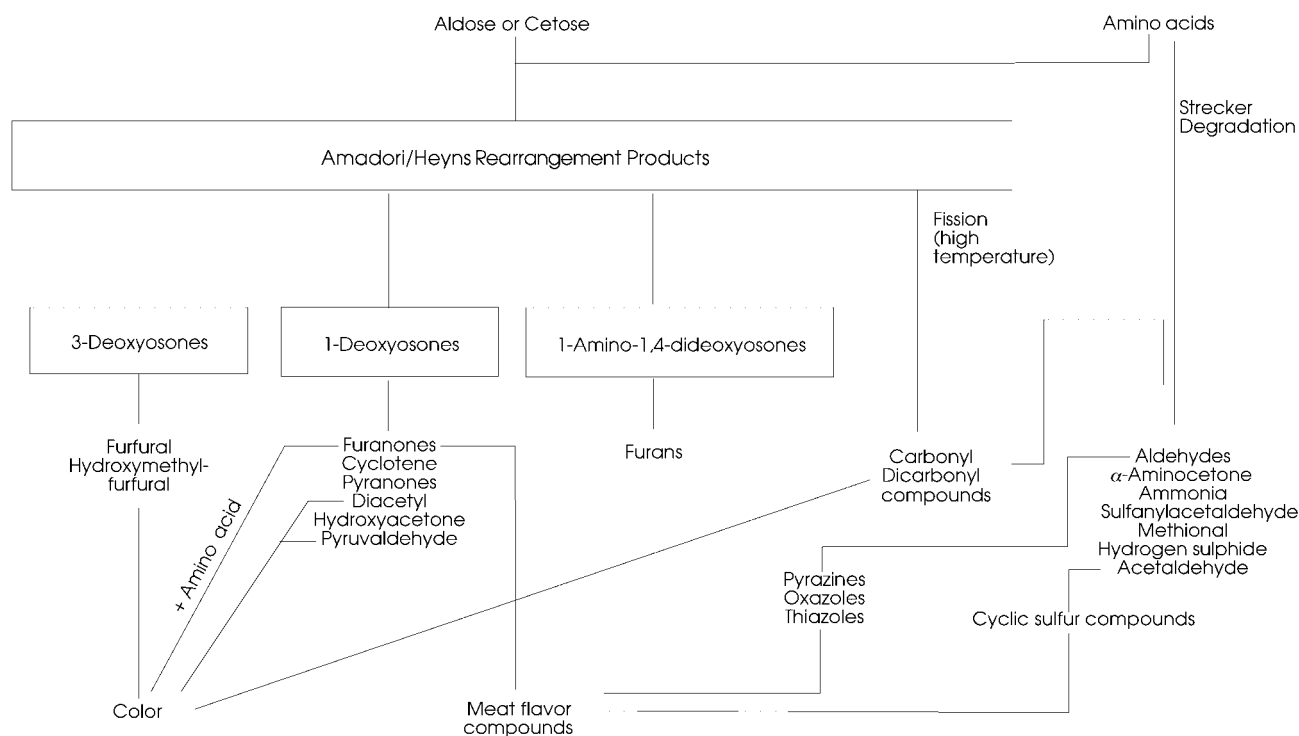


Figure 1. Pathways of formation of key flavor intermediates and products in the Maillard reaction. Osone is the former name of the 2-aldoketoses that could be prepared by the hydrolysis of osazones. Cyclotene = 2-hydroxy-3-methyl-2-cyclopenten-1-one.

culinary arts depends on this supporting work of molecular gastronomy.

A result of such explorations? There are many. For example, it has been written, with no explanation, by the French cook Auguste Escoffier (1846–1935) that red berries should not be put into copper pans or vessels coated with tin.<sup>[12]</sup> But if you just put raspberries in a pan with a tin coating, no visible change occurs. Would copper have an influence? Adding metallic copper to the fruits makes again no visible change. Of course there is a possibility that Escoffier repeated a previous false culinary indication, but molecular gastronomists have to be conscious that some cooks are very good observers. And it is known from chemistry textbooks that anthocyanidins can bind to metal ions, which results in a shift of the absorption towards the blue region of the spectrum.<sup>[13]</sup> Could metal ions inside pans be responsible for a change? The experiment of adding various metal ions to raspberries (about 0.01 g of metal salt per gram of fruit) shows that with  $\text{Sn}^{2+}$  ions raspberries turn such a dark purple color that the fruits seem spoiled or toxic!<sup>[14]</sup> The conclusion is that over half a century ago the vessels were probably, by today's standards, very dirty: Escoffier's advice was probably right at Escoffier's time, but today the advice should be modified and made more precise: never put red berries in a dirty tin-coated vessel otherwise the berries turn purple.

There are many other examples of the usefulness of chemistry in the kitchen. As for culinary advice, all possibilities occur: some advice seems trustworthy, and is correct, some seems trustworthy and is wrong, some seems wrong and is correct, and some seems wrong and is wrong (e.g. the

mayonnaise and the periods of women: even this has been tested!).

## 2. Understanding Culinary Processes and Recipes

Investigations of culinary processes or know-how lead naturally to explorations of recipes, and in some cases to proposals for rationalization and “improvements”; this is the second aim of molecular gastronomy.

Let us examine one example: cheese soufflés. The basic ingredients are a viscous preparation, such as a béchamel sauce (made from melted butter, flour, and milk) to which, when at room temperature (or higher, but below 68 °C), grated cheese, egg yolks, and whisked egg whites are added.<sup>[15]</sup> The swelling of soufflés during cooking has been attributed to thermal dilatation of air bubbles from the whipped egg whites<sup>[16]</sup> but this model is clearly defective: using the data from measurements of the temperature and the pressure inside a soufflé (see Figures 2a and b), the ideal gas law predicts a maximum swelling of 20 %, however, the volume of soufflés can double or more! Indeed the main effect is water evaporation: in contact with the ramekin walls (the walls of the container), the water (mainly from the milk, which is about 88 % water w/w, and from the yolks)<sup>[17]</sup> inside the soufflé base is heated to a temperature equal to the inside temperature of the oven, that is, 180 °C.<sup>[18]</sup> The vapor formed at the top of the soufflé is lost to the oven, but the vapor formed on the bottom of the ramekin pushes the other layers upward. This model thus suggests that soufflés should be heated preferably on the bottom.



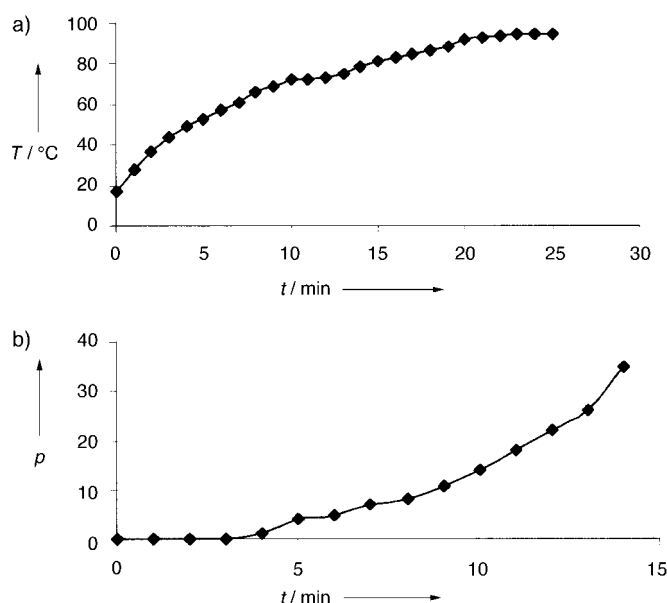


Figure 2. a) The temperature inside a soufflé was measured for 25 min with a thermocouple anchored to the soufflé dish (20 cm diameter and 10 cm deep) with its tip 2 cm from the surface of the mixture at the start. The dish was placed in the preheated oven ( $180^\circ\text{C}$ ), and the soufflé was found to be perfectly cooked when removed from the oven a few minutes after the temperature  $T$  rose to about  $65\text{--}70^\circ\text{C}$ . Of course, the temperature is always lower than  $100^\circ\text{C}$  (otherwise, the soufflé would have been transformed into a crackling pancake). b) The pressure  $P$  [mm oil] inside a soufflé measured during the time  $t$  the soufflé was cooked. The pressure was measured using a manometer put at the center of a ramekin.

All soufflé recipes emphasize that it is important to mix the whipped egg white thoroughly with the cheese béchamel so that no blobs of egg white remain; the folding in must be done gently so as to prevent the air bubbles from bursting or coalescing. But recipes do not agree about the firmness of the whisked egg white. After preliminary experiments, carried out in 1993,<sup>[19]</sup> we recently measured the effect that the firmness of egg whites has on soufflé preparation. We divided a cheese béchamel into two equal parts, and added to both parts foams of different firmness made from the same egg whites: in the first part, the whites were whisked until the first soft peaks were observed; in the second part the egg whites were so firm that an egg in its shell (62 g) could stand on top of them without sinking. The soufflés were placed in identical ramekins 15 cm diameter, 10 cm deep, filled up to 8 cm. They were cooked in the same oven (De Dietrich P5447), at the same time, and the volume of the two soufflés was compared (Figure 3).

There are two reasons for the differences. The first is a result of the difference in initial volume: differently whipped egg whites have different volumes. Second it is observed that when a soufflé with soft egg whites is cooked vapor bubbles go up, through the viscous soufflé preparation and burst at the upper surface of the soufflé; however, in the soufflé with firm egg whites, the firmness of the foam prevents (partially) the bubble from going through the soufflé preparation and the upper layers are pushed upwards.

Finally this model and a simple measurement shows that huge improvements in soufflé making are possible: a 345 g



Figure 3. These two cheese soufflés have the same composition, but in the one on the right, the egg whites were much firmer, hence the difference in final volume.

soufflé cooked in a traditional way loses about 10 g of water during cooking, which means that a volume of about 10 L could be obtained if the upper surface were made vapor proof!

This example shows how modeling leads to improvement of traditional recipes. Another example shows that modeling leads also to a rationalization of recipes. Many cooks begin their sauce preparation by “reducing dry” shallots with wine (in other words, complete evaporation of the wine).<sup>[20]</sup> Why do they boil and evaporate completely a costly liquid? Experiments with various wines show that different results are possible: because of composition differences of grapes and different wine-making methods, some wine have more non-evaporable compounds (glucose, fructose...) than others,<sup>[21]</sup> and boiling wines leads either to cooked shallots in an empty pan or in a thick brown syrup. There are many reasons for the formation of this viscous liquid. First, wine contains compounds that do not evaporate in the conditions of boiling: the ash content of wines is about  $2\text{ g L}^{-1}$ .<sup>[22]</sup> Second, amino acids (about  $200\text{--}800\text{ mg L}^{-1}$ ) can react through Maillard reactions with reducing sugars (the carbohydrates ( $0.03\text{--}0.5\%$ ) present in fully fermented wine are small amounts of the hexoses, glucose and fructose, and of nonfermentable pentoses, such as arabinose, rhamnose, xylose; incompletely fermented wines contain higher concentrations of both hexoses, but substantially more of the slower fermenting fructose). Third, carbohydrates, such as glucose and other sugars can make caramels,<sup>[23]</sup> as the temperature reached in white wine that is boiled until the volume is 1 % of the initial volume is as high as  $130^\circ\text{C}$ .<sup>[24]</sup> Finally, a sensory comparison of shallots cooked under five sets of conditions (first done during the Second International Workshop on Molecular Gastronomy, Erice, Italy, may 1995) suggests that caramelization of glucose and fructose could give a better base for a good béarnaise than the product made by boiling an expensive wine (and evaporating most of its flavors); the conditions were: 1) with pure water, 2) with water and glucose, 3) with a poor dry wine, 4) with the same wine plus  $10\text{ g L}^{-1}$  of glucose or fructose, 5) with a good wine, such as a Noilly.

This result has culinary significance: a cook who wants to make a sauce and does not know in advance the composition of the wine he or she is using could cook some glucose or fructose with water and shallots,<sup>[25]</sup> thus making a caramel that will give a strong taste and flavor to the sauce.

This idea was applied by the three-star cook Pierre Gagnaire (Restaurant Pierre Gagnaire, Paris, France) in one dish of the “Science and Cooking” menu that was served in March 2000 at the French Academy of Sciences, during a lecture on molecular gastronomy (“the proof is in the pudding, isn’t it?”). Of course wine boiling should be investigated further to give new ideas of the chemistry that could be used as a start for other “chemically modified béarnaise”.

### 3. New Products, New Tools, New Methods

There is room for much improvement in culinary practices. New products, new tools, and new methods could be usefully introduced into the kitchen.

Let us consider first the question of ingredients. Cooks are trained at using spices and herbs in their kitchen; in the laboratory, chemists also use, on a daily basis, fragrant products such as hexanal, *trans*-hexenal, 1-hexanol, 1-octen-3-ol, or benzyl *trans*-2-methylbutenoate. Could we use these chemicals in the kitchen? Very easily. If you cannot afford a very good olive oil, try hexanal in poor oil! If you do not have wild mushrooms, put some 1-octen-3-ol or benzyl *trans*-2-methylbutenoate in your dishes (these two compounds have, at the appropriate doses, a wonderful mushroom or forest taste). If you want to make some pastry with a violet flavor, use beta-ionone. If you cannot afford the price of a very good whisky, try adding some drops of vanillin solution<sup>[26]</sup> to a cheap whisky and you will see how the whisky becomes “round”: the idea is only to replace the slow reactions that take place in the barrels, where ethanol extracts some lignin from the wood and reacts with it, forming various aldehydes (sinapic (4-hydroxy-3,5-dimethoxycinaldehyde), vanillic (4-hydroxy-3-methoxybenzaldehyde), syringic (4-hydroxy-3,5-dimethoxybenzaldehyde)).<sup>[27]</sup> There are lots of chemicals that could be used to modify the taste of the dishes, and some others could be useful in managing texture.

Hence a question: how is it that domestic cooks generally fear the additives that are used by the food industry? Probably they fear what they do not know: if chemists have the feeling that these products are safe and useful they should ask that these compounds should be presented to the public, as well as their effects. And it would be probably a good idea to sell these products to the domestic cooks, so that they could be used to them: instead of using a whole lemon to prevent apple slices browning as a result of polyphenoloxidase enzymes, some drops of a ascorbic acid solution of the same concentration as lemon juice is as efficient and cheaper.

Cooks could also use new tools. Chemistry laboratories are full of well-designed hardware that could improve culinary preparations. If you filter with a Büchner funnel, for example, you will get a much clearer stock than if you use a culinary sieve. A glass column over a fritted glass makes easy foams, by injection of air under the fritted glass. Ultrasound boxes can make emulsions in seconds. Separating funnels can be used to separate aromatic (fragrant) molecules: if oil, water, and a tasty ingredient (mushroom, spice) are put in a bulb, the molecules responsible for flavor will be separated according to their different solubility in the two liquids, so that the cook

will get two tastes from one. A reflux column, also, could retain the flavors over the pans better than lids.<sup>[28]</sup>

Eventually cooks will have to use new methods if they use new tools and new ingredients. But we have time as change will probably be very slow: in 1894, during a discourse at a banquet of the chemical industry, the French chemist Marcelin Berthelot envisioned a future where agriculture and cooking have disappeared, because of progress in chemistry; pills, he proposed, would have replaced dishes.<sup>[29]</sup> One century later, we still cook choucroute, soufflés, béarnaise, foie gras, and grilled lobsters. However, in our times, important questions of interactions of health and food arise. To deal with these complicated issues, one cannot only analyze foods from the toxicological or nutritional point of view: a detailed analysis of practices is important to know which compounds can be found in the real diet of the public.

For example, the public is seldom able to cook meat safely with a fire: nowadays in barbecues, the meat is most frequently placed directly over the fire, at a distance such that the amount of benzo[*a*]pyrenes—a carcinogenic compound the concentration of which should not exceed 1 µg kg<sup>-1</sup> end product<sup>[30]</sup>—is as high as 10 µg kg<sup>-1</sup>!<sup>[31]</sup> But if the meat is placed 5 cm higher, the benzo[*a*]pyrene content is reduced to about 0.7 µg kg<sup>-1</sup>, and if the meat is placed before the fire instead of above, as was recommended by most old culinary books, the quantity of these compounds is reduced to 0.1 µg kg<sup>-1</sup>, which is the natural content of the product.

### 4. Inventing New Dishes

All the studies in molecular gastronomy easily lead to new dishes. How successful will they be? One way to have them used would be to prepare them with the aid of only tools or ingredients already present in the kitchens. For example, the separating funnel used to separate flavors can be replaced by a simple jam pot with a lid (but what a pity!).

Another example: the analysis of the preparation of Chantilly cream suggests a transposition of the process.<sup>[32]</sup> In its principle, the process is the foaming of an emulsion (cream is an emulsion, and whipped cream is an hybrid system, both an emulsion and a foam; Chantilly cream is whipped cream with sugar). How can we make the transposition? Let us remark first that, if we heat chocolate and water together, we get a chocolate emulsion that could be named “chocolate béarnaise”, because the process is the same as a classical béarnaise preparation: water is substituted for vinegar, lecithin present in the chocolate for egg proteins, and cocoa butter for milk butter. Whipping this chocolate béarnaise (first put the pan on ice cubes for faster results) finally generates foam. This foam is brown, but of a lighter color than the original emulsion. Its texture is the same as whipped cream, if the proportions are correct, that is, about 225 g of chocolate for 200 mL of water (the exact proportions depends on the kind of chocolate used). We named this foam “Chantilly chocolate”.

The same process can be applied to other products containing a large amount of lipids. For example, one can make “Reblochon Chantilly” with Reblochon cheese, “Roquefort Chantilly” with Roquefort cheese, “Munster Chan-

tilly" with Munster cheese or even a foie gras chantilly with foie gras.

Another more recent example shows how pure science can lead to new dishes. Let us begin with the concept of emulsion. The most famous emulsion, in the kitchen, is the mayonnaise, a sauce traditionally made with some water (from the egg yolk, from the vinegar, and from the mustard if used), surfactants (egg yolk proteins, but also egg phospholipids), and oil.

Let us first note that a "mayonnaise without yolk" can be made with egg white: while whipping an egg white, add oil.<sup>[33]</sup> Another variation of this theme is the "mayonnaise without egg": heat some "water" (or any water solution; it can be a very good lobster "fond"), dissolve half a gelatine sheet and add some oil as you whip the mixture. A white emulsion is formed that slowly jellifies. Under the microscope, the oil droplets fuse locally, and finally an emulsion is trapped into a gel (see Figure 4). This gel is a result of gelatine molecules that form segments of triple helices.<sup>[34–36]</sup> Now consider the general phenomenon that took place: an emulsion was trapped into a

physical gel. Could the same phenomenon be observed but with a chemical gel? The test is easy: take the mayonnaise with egg white, and put it in the microwave oven for one or two minutes; the heating generates a semi-solid mass, where the emulsion can still be seen under the microscope and characterized by small angle X-ray diffraction.

You think that this oil dispersion is not very pleasant on your table? Replace the oil with melted chocolate, and you get a chocolate cake in one minute: of interest is the very tender texture, because the chocolate is melted, and the powerful aroma, because of the high temperature of the chocolate. I propose to name this dish a "chocolate dispersion" because chocolate is dispersed twice: once in the emulsion, and one in the chemical gel.<sup>[37]</sup>

## 5. Science and the Citizen

All the four first aims of molecular gastronomy are intended to benefit the lay person that cooks. He or she is gaining from the results of the explorations or innovations based on the molecular understanding of culinary processes. He or she is being presented with new methods, tools, or ingredients. He or she is being shown that sciences are wonderful intellectual tools to understand the world we live in. The final aim of molecular gastronomy is to end the bad public image that sciences have too often, mostly during food crises (epidemics of mad cow disease, affairs of dioxin-contaminated chickens).

If we can show that cooking is just chemistry and physics, the public will have to conclude that sciences are not bad, in fact will be able to make useful distinctions between science, the marvelous intellectual activity, and the applications of science, the responsibility of which rests with those who use it.

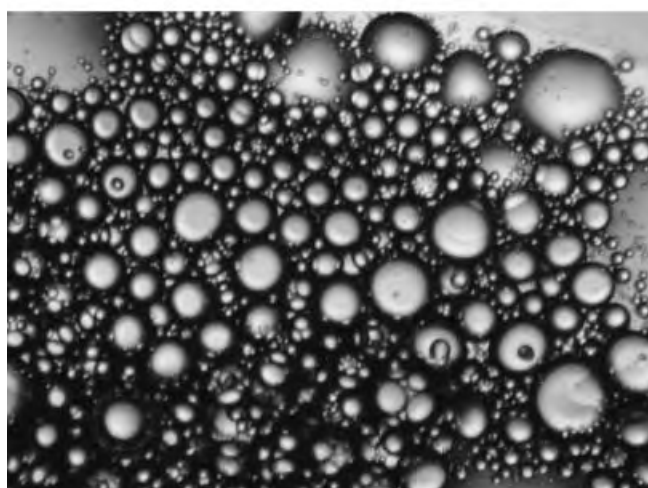
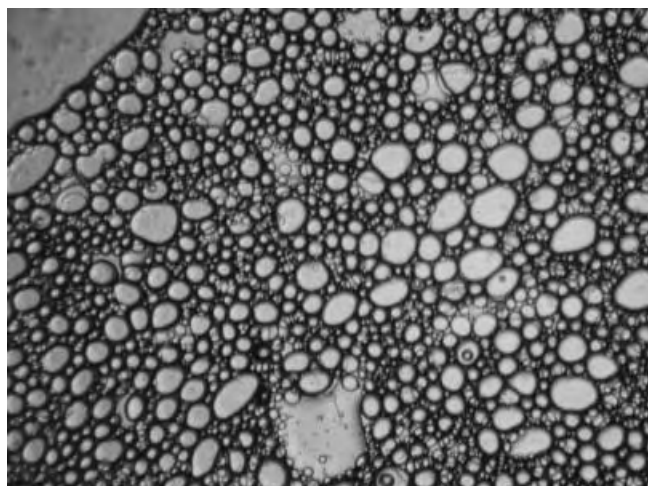


Figure 4. Top: The microscopic structure of an emulsion made from water, gelatine and oil, immediately after the preparation. Bottom: some minutes after preparation (depending on the process and environment) the emulsion gellifies. The result is an emulsion trapped into a physical gel.

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- [2] H. This, *Manger magique*, Revue Autrement, Paris, **1996**.
- [3] Auguste Escoffier (*Le guide culinaire*, Flammarion, Paris, **1921**, p. 48) describes the preparation of the mayonnaise sauce as follows: 1. Broyer au fouet six jaunes d'oeufs dont le germe doit être retiré; un litre d'huile, 10 grammes de sel, un gramme de poivre blanc; une cuillère et demie de vinaigre, ou l'équivalent de jus de citron si on veut l'obtenir très blanche. 2. Ajouter l'huile goutte à goutte pour commencer, et al laisser tomber ensuite en petit filet dans la sauce quand celle-ci commence à se lier. 3. Rompre le corps de la sauce de temps en temps par addition de vinaigre ou de jus de citron. 4. Additionner finalement la sauce de 3 cuillères d'eau bouillante; ce qui a pour but d'en assurer la cohésion et de prévenir sa décomposition si elle doit être tenue en réserve. English translation: with a whisk, "grind" six egg yolks whose germ has to be taken away, plus salt (10 grams), pepper (one gram), half a tea spoon of vinegar; add one liter of oil drop by drop in the beginning, and faster later, when the sauce has some firmness; add some vinegar or lemon juice from time to time, and finally add 3 spoons of boiling water that will increase the cohesion and prevent the decomposition of the sauce if it is to be kept for some time.
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- [12] A. Escoffier, *Guide culinaire*, Flammarion, Paris, **1921**.
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- [14] H. This, *Thèse de doctorat ès sciences*, University Paris VI, **1996**.
- [15] In all our experiments, we used the same proportions: a "roux" was prepared with flour (75 g), butter (75 g); the mixture was heated up to 100 °C, and, when a homogeneous paste was obtained, milk (400 mL) was added; after this mixture thickened by slow cooking (the thickness is because of starch granules swelling when they absorb water), after the mixture had cooled to room temperature grated cheese (50 g) and four egg yolks were added. The four egg whites were whipped separately and thoroughly mixed into the cheese béchamel.
- [16] *Larousse gastronomique*, Larousse, Paris, **1982**.
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- [23] J. Defaye, J. M. Garcia Fernandez, *Zuckerindustrie* **1995**, *120*, 1.
- [24] For this measurement, we used a low price white wine, "Special Marée blanc de blancs" from Les Celliers de Haute Croix, Prabeq (France).
- [25] For example fructose (10 g) in water (5 mL).
- [26] In many lectures, we used "Extrait de vanille liquide", *Vahiné*, a product sold in every French supermarket, but any other similar product could be used instead; (you should not be able to smell the vanillin in this experiment; adjust your particular vanillin solution so that the concentration in vanillin is just lower than the smell perception threshold).
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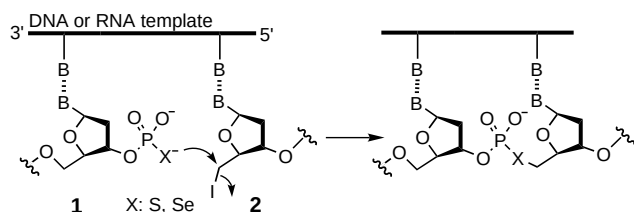
# DNA-Templated Synthesis: More Versatile than Expected

Daniel Summerer and Andreas Marx\*

It has been known for almost twenty years that nucleic acids may promote chemical reactions. Catalytic nucleic acids can be found in nature or evolved through in vitro selection processes.<sup>[1]</sup> Structural and functional investigations suggest that catalytically active nucleic acids act in a similar manner to enzymes: they promote chemical reactions through the precise spatial alignment of the reaction partners, the stabilization of transition states, and binding of reaction products in an elaborate manner.<sup>[1]</sup> Recent reports reveal new facets of nucleic acid promoted chemistry and indicate that DNA strands are able to promote chemical reactions by bringing reaction partners in close proximity of each other rather than by precisely aligning the reactive groups. Herein we focus on recent progress made in this diverse field.<sup>[2]</sup> For deeper insights we refer to the literature cited in the references.

The ability of nucleic acid templates to promote coupling of adjacently annealed reaction partners to form the corresponding ligation products has been known.<sup>[3]</sup> This feature has been exploited in the race for the development of new and efficient methods for the detection of nucleotide variations such as single nucleotide polymorphisms (SNPs) in genes. Kool and co-workers have reported chemical autoligation processes, including the reaction of a phosphothioate or -selenoate anion **1** on one strand with a 5'-carbon atom **2** that bears an iodide leaving group on the other strand (Scheme 1).<sup>[4]</sup>

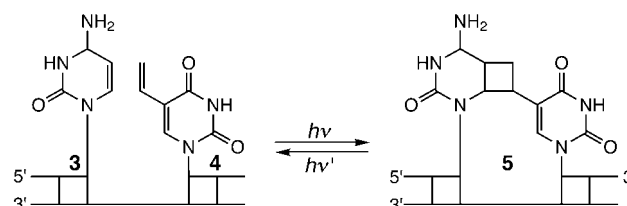
Efficient ligation is only observed when complementary templates are applied for the binding of the oligonucleotide reagents **1** and **2**. Mattes and Seitz recently demonstrated that



Scheme 1. Chemistry of the phosphothioate and -selenoate autoligation of DNA.<sup>[4]</sup> B = nucleobase.

two modified peptide nucleic acid (PNA) strands that are complementary to an adjacent DNA target sequence can be sequence-specifically ligated.<sup>[5]</sup> These results indicate that sequence specificity is not limited to a DNA phosphodiester backbone.

Saito and co-workers reported the photoreversibility of DNA-mediated ligation of oligonucleotides through 5-vinyldeoxyuridine (Scheme 2).<sup>[6]</sup> The different photochemical properties of the starting materials **3** and **4** and of the [2+2] adduct **5** facilitates switching between ligation and the reverse process. The authors suggest that this photoligation approach may find applications in DNA engineering and nanotechnology.

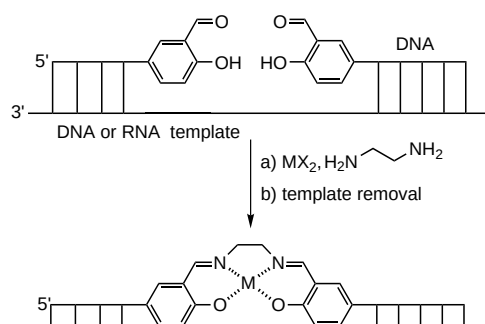


Scheme 2. DNA-templated photoreversible ligation of oligonucleotides through 5-vinyldeoxyuridine.<sup>[6]</sup> DNA double stranded regions are represented as a ladder for simplicity.  $h\nu$ :  $\lambda = 366$  nm,  $h\nu'$ :  $302$  nm.

A new aspect of DNA-templated synthesis was described by Czapinski and Sheppard, who reported the assembly of metallosalen–DNA conjugates. These compounds provide a new class of metal–DNA hybrids, which are potentially useful for targeted nucleic acid cleavage or for the development of biosensors (Scheme 3).<sup>[7]</sup> The formation of these assemblies is presumably driven by several template effects. First, two salicylaldehyde moieties of modified oligonucleotide reagents are brought into close proximity of each other by a complementary DNA template. The resulting complex in turn serves as a template for binding a metal ion ( $\text{Mn}^{\text{II}}$ ,  $\text{Ni}^{\text{II}}$ ), which subsequently drives salen formation as a result of a metal-templated reaction between the aldehydes and ethylenediamine.

A recent publication by Gartner and Liu indicated that DNA is able to direct chemical reactions sequence-specifically in a more versatile way than was previously thought.<sup>[8]</sup> Two different DNA architectures, helix terminus (**T**) and hairpin (**H**), were equipped with electrophiles and treated with nucleophiles linked to a complementary DNA oligonucleotide (Figure 1). Both approaches led to the formation of

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Scheme 3. Nucleic acid templated metallosalen-DNA assembly.<sup>[7]</sup> M = Mn<sup>II</sup>, Ni<sup>II</sup>.

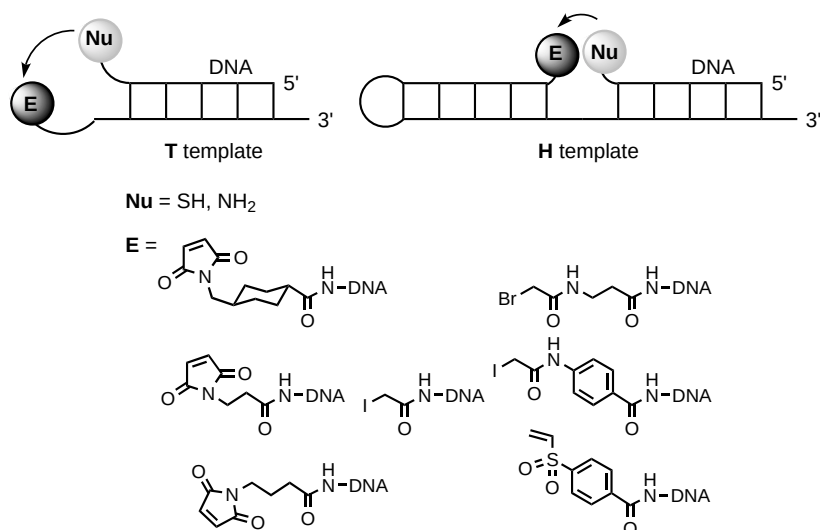
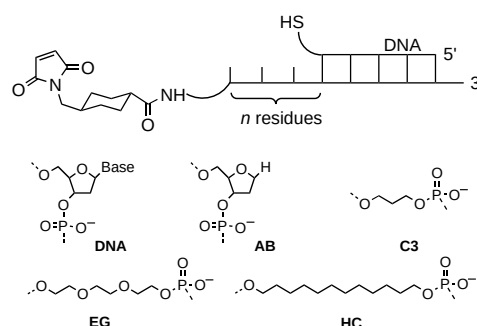


Figure 1. Synthesis directed by helix terminus (T) and hairpin (H) templates.<sup>[8]</sup> E = electrophile, Nu = nucleophile, DNA double stranded regions are represented as a ladder for simplicity.

the expected reaction products, whereas little non-templated intermolecular product formation was observed. Remarkably, the reported DNA-templated reactions include a variety of reaction types and reactant structures, despite considerable variations in their transition-state geometry, steric hindrance, and conformational flexibility.

Interestingly, it was found that single nucleobase mismatches introduced in the DNA duplex caused a more than hundred-fold decrease in the reaction rate. However, the origins for the almost ubiquitous sequence selectivity in the DNA-templated reactions remains to be fully elucidated. Gartner and Liu further investigated how the length and the nature of the linkers that bear the reactants influence product formation (Scheme 4). Reactants that were separated by only one base reacted with rates similar to those that were separated by up to 30 bases, while maintaining sequence specificity. Furthermore, templates in which the linking nucleotides were replaced with any of the alternatives shown in Scheme 4, had little effect on the rates of product formation, which indicates that structural elements of DNA are not responsible for the observed distance independence. The sequence specificity and distance independence suggest that mixtures of reagents may be able to react predictably with complementary mixtures of templates. In future, it should be possible to program chemical reactions in a ordered and predictable



Scheme 4. Distance dependence of DNA-templated synthesis.<sup>[8]</sup> Investigated constructs: n = 1–30 (DNA), 9 (AB), 9 (C3), 6 (EG), 5–6 (HC).

fashion by attachment of a DNA sequence as a specific reaction tag. Gartner and Liu have reported the first promising results along this line. Nevertheless, the general applicability of this approach remains to be established.

The described developments suggest that DNA-templated synthesis is a phenomenon that applies to a remarkable variety of chemical reactions and may be more general in nature. The ease of automated DNA synthesis, predictable binding, and established methods for nucleic acid amplification and sequence analysis render DNA a promising template for future developments and applications. DNA-templated synthesis is still an emerging field with a great potential for further advancements in organic and supramolecular synthesis, combinatorial chemistry, and biotechnology.

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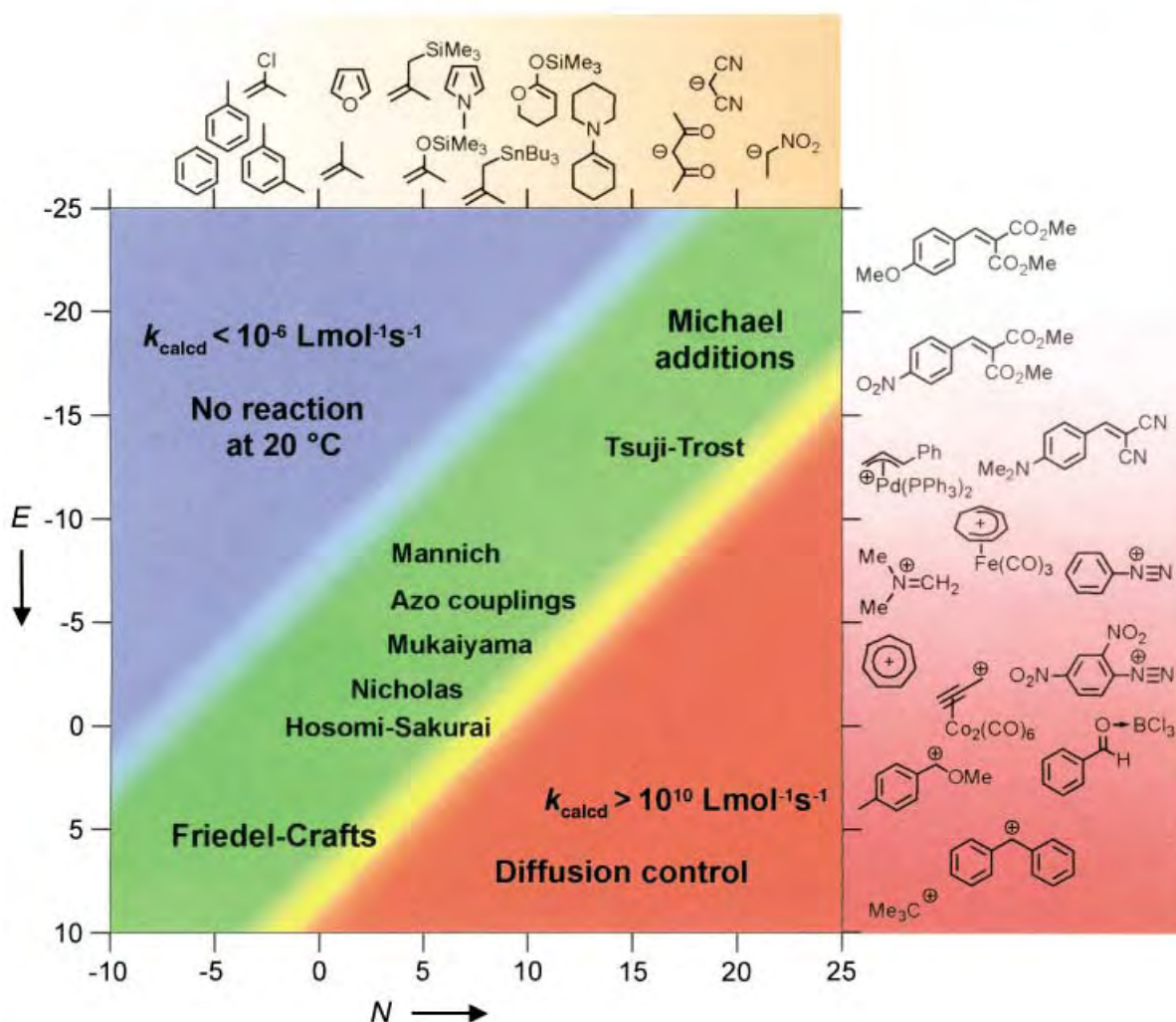


The kinetics of carbocation–carbanion combinations have been the missing link for a comprehensive model of polar organic reactivity.

$$\log k_{20^\circ\text{C}} = s (N + E)$$

$N$  = nucleophilicity  
parameter  
 $s$  = slope parameter ( $\approx 1$ )

$E$  = electrophilicity  
parameter



The following pages show why only two parameters ( $E$  and  $N$ ) are sufficient for a semiquantitative prediction of the rates of many polar organic reactions.

# Kinetic Studies of Carbocation–Carbanion Combinations: Key to a General Concept of Polar Organic Reactivity\*\*

Roland Lucius, Robert Loos, and Herbert Mayr\*

Dedicated to Professor Lutz F. Tietze  
on the occasion of his 60th birthday

Organic chemistry is usually organized by the concept of functional groups. Although electrophile–nucleophile interactions are recognized as the key elements of many synthetic transformations, for example, electrophilic and nucleophilic aromatic substitutions as well as electrophilic and nucleophilic additions to ethylene derivatives and metal  $\pi$  complexes, these examples are usually treated as separate, seemingly unrelated reactions. This background explains the enthusiastic acceptance of qualitative perturbation molecular orbital theory (PMO theory), which treats a wide variety of organic reactions with a single principle: the interaction of the highest occupied molecular orbital of one reagent with the lowest unoccupied molecular orbital of the other.<sup>[1]</sup> Despite the wide applicability of PMO theory, quantitative predictions of rate constants can only be made within restricted series of reactions.

We recently showed that a modified linear free energy relationship approach [Eq. (1);  $s$  = nucleophile-specific slope parameter,  $N$  = nucleophilicity parameter,  $E$  = electrophilicity parameter], which employs benzhydryl cations (diaryl carbenium ions) as reference electrophiles, can be used to set up a general reactivity scale for  $\pi$  nucleophiles, including substituted benzenes and heteroarenes, alkenes, enol ethers, allylsilanes and -stannanes, ketene acetals, and enamines.<sup>[2a]</sup> Equation (1) even provides a direct comparison of  $\pi$ ,  $n$ , and  $\sigma$  nucleophiles.<sup>[2]</sup>

$$\log k (20^\circ\text{C}) = s(N + E) \quad (1)$$

Although previous applications of Equation (1) were restricted to the reactions of cationic electrophiles with uncharged nucleophiles,<sup>[2]</sup> the reactions of carbanions with uncharged electrophiles were found to follow a similar pattern.<sup>[3]</sup> We now report the kinetics of the reactions of highly stabilized carbocations **1a–f** with carbanions **2a–g** ([Eq. (2), Table 1, and Table 3) and show that these data can be used to construct reactivity scales that combine the chemistry of carbocations with that of carbanions.<sup>[4, 5]</sup>

The fast reactions were investigated by using stopped-flow techniques with photometric detection of the blue carbocations **1a–f**. Usually, solutions of **1–BF<sub>4</sub>** ( $10^{-6}$ – $10^{-5}$  M) in dimethyl sulfoxide (DMSO) were combined with solutions of

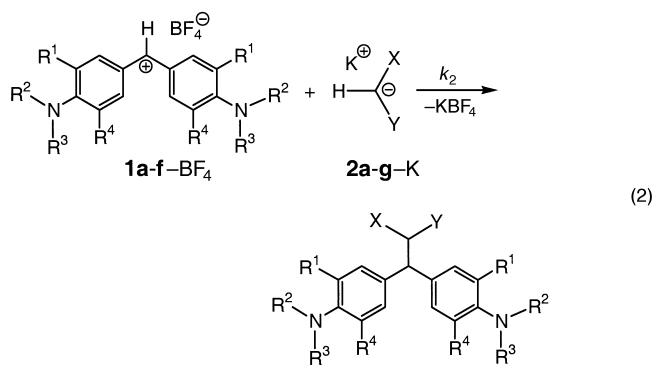


Table 1. Substitution pattern and electrophilicity parameters of the benzhydryl cations **1a–f** [Eq. (2)].

|           | R <sup>1</sup> | R <sup>2</sup>                                     | R <sup>3</sup>                                     | R <sup>4</sup> | E <sup>[a]</sup> |
|-----------|----------------|----------------------------------------------------|----------------------------------------------------|----------------|------------------|
| <b>1a</b> | H              | CH <sub>3</sub>                                    | CH <sub>3</sub>                                    | H              | – 7.02           |
| <b>1b</b> | H              | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) | H              | – 7.69           |
| <b>1c</b> |                | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) | CH <sub>3</sub>                                    | H              | – 8.22           |
| <b>1d</b> |                | (CH <sub>2</sub> CH <sub>2</sub> )                 | CH <sub>3</sub>                                    | H              | – 8.76           |
| <b>1e</b> |                | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) |                | – 9.45           |
| <b>1f</b> |                | (CH <sub>2</sub> CH <sub>2</sub> )                 | (CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) |                | – 10.04          |

[a] Electrophilicity parameters taken from ref. [2a].

**2–K** ( $10^{-5}$ – $10^{-4}$  M) that contained [18]crown-6 (1.01–1.10 equivalents). Since in all cases a **[2]/[1]** ratio greater than ten was chosen, the almost constant carbanion concentration gave rise to pseudo-first-order kinetics, which was deduced from the exponential decay of the carbocation absorbance at  $\lambda_{\text{max}}$  (DMSO) = 616–643 nm.

From the ion-pair dissociation constants of the potassium salts **2–K** in DMSO,<sup>[6]</sup> one can derive that ion pairing is negligible at the concentrations of the kinetic experiments, in accord with our previous report that the same rate constants were found for the reactions of **1j** (Table 2) with **2f–NBu<sub>4</sub>**, **2f–K**, **2f–K**/[18]crown-6, and **2f–K**/Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane).<sup>[3]</sup> For that reason, the observed pseudo-first-order rate constants can be divided by the carbanion concentration to give the second-order rate constants  $k$  (Table 3). The high oxidation potentials of the carbanions **2b–g**,<sup>[7a,b]</sup> indicate that the

Table 2. Structural formula and electrophilicity parameters of the quinone methides **1g–m**.

|           | Y                                | X                                | E <sup>[a]</sup> |
|-----------|----------------------------------|----------------------------------|------------------|
| <b>1g</b> | OCH <sub>3</sub>                 | Br                               | – 8.63           |
| <b>1h</b> | OCH <sub>3</sub>                 | C <sub>6</sub> H <sub>5</sub>    | – 12.18          |
| <b>1i</b> | N(CH <sub>3</sub> ) <sub>2</sub> | C <sub>6</sub> H <sub>5</sub>    | – 13.39          |
| <b>1j</b> | CH <sub>3</sub>                  | C(CH <sub>3</sub> ) <sub>3</sub> | – 15.83          |
| <b>1k</b> | OCH <sub>3</sub>                 | C(CH <sub>3</sub> ) <sub>3</sub> | – 16.11          |
| <b>1l</b> | N(CH <sub>3</sub> ) <sub>2</sub> | C(CH <sub>3</sub> ) <sub>3</sub> | – 17.29          |
| <b>1m</b> | <sup>[b]</sup>                   | C(CH <sub>3</sub> ) <sub>3</sub> | – 17.90          |

[a] Electrophilicity parameters from correlation analysis in this work. [b] Y–C<sub>6</sub>H<sub>4</sub> = Julolidin-9-yl (Figure 1).

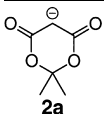
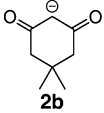
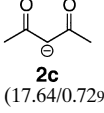
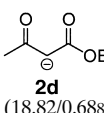
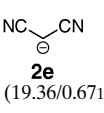
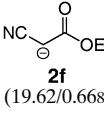
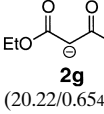
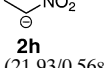
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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Table 3. Experimental second-order rate constants  $k$  (20 °C) and calculated values  $k_{\text{calcd}}$  from Equation (1) for the reactions of electrophiles **1a–i** with carbanions **2a–g**.<sup>[a]</sup>

| Nucleophile( <i>N</i> / <i>s</i> )                                                                                | Electrophile                            | $k$ [L mol <sup>-1</sup> s <sup>-1</sup> ] <sup>[b]</sup> | $k_{\text{calcd}}$ [L mol <sup>-1</sup> s <sup>-1</sup> ] <sup>[c]</sup> |
|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------|
| <br><b>2a</b><br>(13.91/0.856)   | <b>1a</b> –BF <sub>4</sub> <sup>–</sup> | $(5.78 \pm 0.07) \times 10^5$                             | $7.84 \times 10^5$                                                       |
|                                                                                                                   | <b>1b</b> –BF <sub>4</sub> <sup>–</sup> | $(2.57 \pm 0.03) \times 10^5$                             | $2.09 \times 10^5$                                                       |
|                                                                                                                   | <b>1c</b> –BF <sub>4</sub> <sup>–</sup> | $(7.37 \pm 0.05) \times 10^4$                             | $7.34 \times 10^4$                                                       |
|                                                                                                                   | <b>1d</b> –BF <sub>4</sub> <sup>–</sup> | $(2.17 \pm 0.01) \times 10^4$                             | $2.55 \times 10^4$                                                       |
|                                                                                                                   | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(7.42 \pm 0.10) \times 10^3$                             | $6.50 \times 10^3$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(2.56 \pm 0.01) \times 10^3$                             | $2.05 \times 10^3$                                                       |
|                                                                                                                   | <b>1g</b>                               | $(3.50 \pm 0.08) \times 10^4$                             | $3.28 \times 10^4$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(2.37 \pm 0.11) \times 10^{1[d]}$                        | $3.03 \times 10^1$                                                       |
|                                                                                                                   | <b>1i</b>                               | $3.08 \pm 0.05$                                           | 2.80                                                                     |
| <br><b>2b</b><br>(16.27/0.767)   | <b>1a</b> –BF <sub>4</sub> <sup>–</sup> | $(1.24 \pm 0.02) \times 10^7$                             | $1.24 \times 10^7$                                                       |
|                                                                                                                   | <b>1b</b> –BF <sub>4</sub> <sup>–</sup> | $(5.75 \pm 0.13) \times 10^6$                             | $3.80 \times 10^6$                                                       |
|                                                                                                                   | <b>1c</b> –BF <sub>4</sub> <sup>–</sup> | $(1.76 \pm 0.02) \times 10^6$                             | $1.49 \times 10^6$                                                       |
|                                                                                                                   | <b>1d</b> –BF <sub>4</sub> <sup>–</sup> | $(5.03 \pm 0.06) \times 10^5$                             | $5.76 \times 10^5$                                                       |
|                                                                                                                   | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(1.97 \pm 0.02) \times 10^5$                             | $1.69 \times 10^5$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(6.08 \pm 0.02) \times 10^4$                             | $6.03 \times 10^4$                                                       |
|                                                                                                                   | <b>1g</b>                               | $(5.85 \pm 0.45) \times 10^5$                             | $7.24 \times 10^5$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(8.99 \pm 0.19) \times 10^{2[d]}$                        | $1.38 \times 10^3$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(1.23 \pm 0.03) \times 10^2$                             | $1.63 \times 10^2$                                                       |
| <br><b>2c</b><br>(17.64/0.729)   | <b>1b</b> –BF <sub>4</sub> <sup>–</sup> | $(2.03 \pm 0.30) \times 10^7$                             | $1.78 \times 10^7$                                                       |
|                                                                                                                   | <b>1c</b> –BF <sub>4</sub> <sup>–</sup> | $(6.79 \pm 0.07) \times 10^6$                             | $7.29 \times 10^6$                                                       |
|                                                                                                                   | <b>1d</b> –BF <sub>4</sub> <sup>–</sup> | $(2.52 \pm 0.04) \times 10^6$                             | $2.96 \times 10^6$                                                       |
|                                                                                                                   | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(8.33 \pm 0.09) \times 10^5$                             | $9.23 \times 10^5$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(3.29 \pm 0.01) \times 10^5$                             | $3.46 \times 10^5$                                                       |
|                                                                                                                   | <b>1g</b>                               | $(4.25 \pm 0.45) \times 10^{6[d]}$                        | $3.67 \times 10^6$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(1.01 \pm 0.01) \times 10^{4[d]}$                        | $9.50 \times 10^3$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(1.30 \pm 0.01) \times 10^3$                             | $1.25 \times 10^3$                                                       |
| <br><b>2d</b><br>(18.82/0.688)  | <b>1c</b> –BF <sub>4</sub> <sup>–</sup> | $(1.72 \pm 0.07) \times 10^7$                             | $1.97 \times 10^7$                                                       |
|                                                                                                                   | <b>1d</b> –BF <sub>4</sub> <sup>–</sup> | $(7.15 \pm 0.24) \times 10^6$                             | $8.42 \times 10^6$                                                       |
|                                                                                                                   | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(3.09 \pm 0.05) \times 10^6$                             | $2.80 \times 10^6$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(1.20 \pm 0.02) \times 10^6$                             | $1.11 \times 10^6$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(4.46 \pm 0.06) \times 10^{4[d]}$                        | $3.73 \times 10^4$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(5.48 \pm 0.02) \times 10^3$                             | $5.48 \times 10^3$                                                       |
| <br><b>2e</b><br>(19.36/0.671) | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(4.32 \pm 0.03) \times 10^6$                             | $4.44 \times 10^6$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(1.76 \pm 0.01) \times 10^6$                             | $1.80 \times 10^6$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(6.80 \pm 0.04) \times 10^{4[d]}$                        | $6.59 \times 10^4$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(1.14 \pm 0.01) \times 10^4$                             | $1.02 \times 10^4$                                                       |
| <br><b>2f</b><br>(19.62/0.668) | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(5.89 \pm 0.06) \times 10^6$                             | $6.17 \times 10^6$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(2.40 \pm 0.04) \times 10^6$                             | $2.51 \times 10^6$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(1.05 \pm 0.01) \times 10^{5[c]}$                        | $9.32 \times 10^4$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(1.49 \pm 0.01) \times 10^4$                             | $1.45 \times 10^4$                                                       |
| <br><b>2g</b><br>(20.22/0.654) | <b>1e</b> –BF <sub>4</sub> <sup>–</sup> | $(9.13 \pm 0.23) \times 10^6$                             | $1.10 \times 10^7$                                                       |
|                                                                                                                   | <b>1f</b> –BF <sub>4</sub> <sup>–</sup> | $(4.11 \pm 0.06) \times 10^6$                             | $4.56 \times 10^6$                                                       |
|                                                                                                                   | <b>1h</b>                               | $(2.59 \pm 0.11) \times 10^{5[d]}$                        | $1.81 \times 10^5$                                                       |
|                                                                                                                   | <b>1i</b>                               | $(2.96 \pm 0.08) \times 10^4$                             | $2.93 \times 10^4$                                                       |
| <br><b>2h</b><br>(21.93/0.568) |                                         |                                                           |                                                                          |

[a] The reactions were carried out in DMSO at 20 °C in the presence of [18]crown-6 (1.01–1.10 equiv). The nucleophilicity parameters  $N$  and the slope parameters  $s$  were determined by correlation analysis, as described in the text. [b] The listed rate constants are averages from three to five experiments with different anion concentrations. [c] The values of  $k_{\text{calcd}}$  were calculated with more decimals of  $E$ ,  $N$ , and  $s$  than those indicated in the table. The use of  $E$ ,  $N$ , and  $s$  from Tables 1–3 leads to slightly deviating values. [d] Without the addition of [18]crown-6. [e] The  $N$  and  $s$  parameters of **2h** were derived from its reactivity towards quinone methides (ref. [3]).

reactions occur through a polar mechanism. In contrast to carbocation–carbanion combinations previously investigated,<sup>[8]</sup> single electron transfer processes do not play a role in this case.<sup>[7c]</sup>

To bridge the gap between the weakest cationic electrophile **1f**<sup>[2a]</sup> and the most reactive quinone methide studied so far, **1j**,<sup>[3]</sup> we have also investigated the kinetics of the reactions of the carbanions **2a–g** with the more electrophilic quinone methides **1g–i** (Table 3), which may be considered as highly stabilized benzhydryl cations.<sup>[9]</sup>

All the rate constants of the reactions of carbanions **2a–h** listed in ref. [3] and in Table 3 were used to calculate the  $E$  parameters of quinone methides **1g–m** and the  $N$  and  $s$  parameters of carbanions **2a–h**, as defined by Equation (1). For this purpose,  $\Delta^2$  [Eq. (3)] was minimized.<sup>[10]</sup>

$$\Delta^2 = \Sigma(\log k - \log k_{\text{calcd}})^2 = \Sigma(\log k - s(E + N))^2 \quad (3)$$

The new reactivity parameters were coupled to those previously determined for carbocations and neutral nucleophiles<sup>[2a]</sup> by keeping the  $E$  parameters for the benzhydryl cations **1a–f** constant in the least-squares fit. Thus, the  $N$  and  $s$  parameters for the carbanions **2a–h** as well as the  $E$  parameters for the neutral electrophiles **1g–m** reported herein correspond to the same references as the previously reported scales, that is,  $E = 0.0$  for the bis(*p*-methoxyphenyl)-carbenium ion and  $s = 1.0$  for 2-methyl-1-pentene.<sup>[2a]</sup> The good agreement between the calculated and the experimental rate constants in Tables 3 and S1 in the Supporting Information (standard deviation: factor 1.16) proves that Equation (1) is also suitable for describing the reactivity of the carbanions towards charged and uncharged  $\pi$  electrophiles. The close similarity between the slope parameters for the carbanions (Table 3) and the uncharged  $\pi$  nucleophiles<sup>[2a]</sup> indicates that a change in the charge does not change the mechanism of the interaction.

With the determination of the  $N$  and  $s$  parameters for the carbanions and of the  $E$  parameters for the quinone methides, the reactivity range covered by Equation (1) has been extended to almost 30 orders of magnitude (Figure 1). The transition from carbocation chemistry on the left side of Figure 1 to carbanion chemistry on the right includes a change of the reference solvent from dichloromethane to dimethyl sulfoxide. To refer to free carbanions, dimethyl sulfoxide has also been selected as the reference solvent for carbocation–carbanion combinations. Because the  $E$  parameters of benzhydryl cations determined in CH<sub>2</sub>Cl<sub>2</sub> were adopted unchanged for DMSO, we have defined  $E$  parameters as solvent-independent. As a consequence, the  $N$  and  $s$  parameters depend on the solvent and refer to dichloromethane for neutral  $\pi$  nucleophiles,<sup>[11]</sup> and to dimethyl sulfoxide for carbanions.

Combinations of neutral electrophiles with neutral nucleophiles have not been used for establishing these reactivity scales and the question arises whether the reactivity parameters thus defined can also be used to predict the rate constants for the reactions of neutral electrophiles with neutral nucleophiles. Table S2 and Figure S1 in the Supporting Information show that the rate constants determined for the reactions of quinone methides **1g** and **1h** with piperidinocyclohexene (**3a**) and piperidinocyclopentene (**3b**) in dichloromethane and in DMSO deviate from those calculated by using Equation (1) by less than a factor of 4. It should be noted, however, that larger deviations have to be expected for the

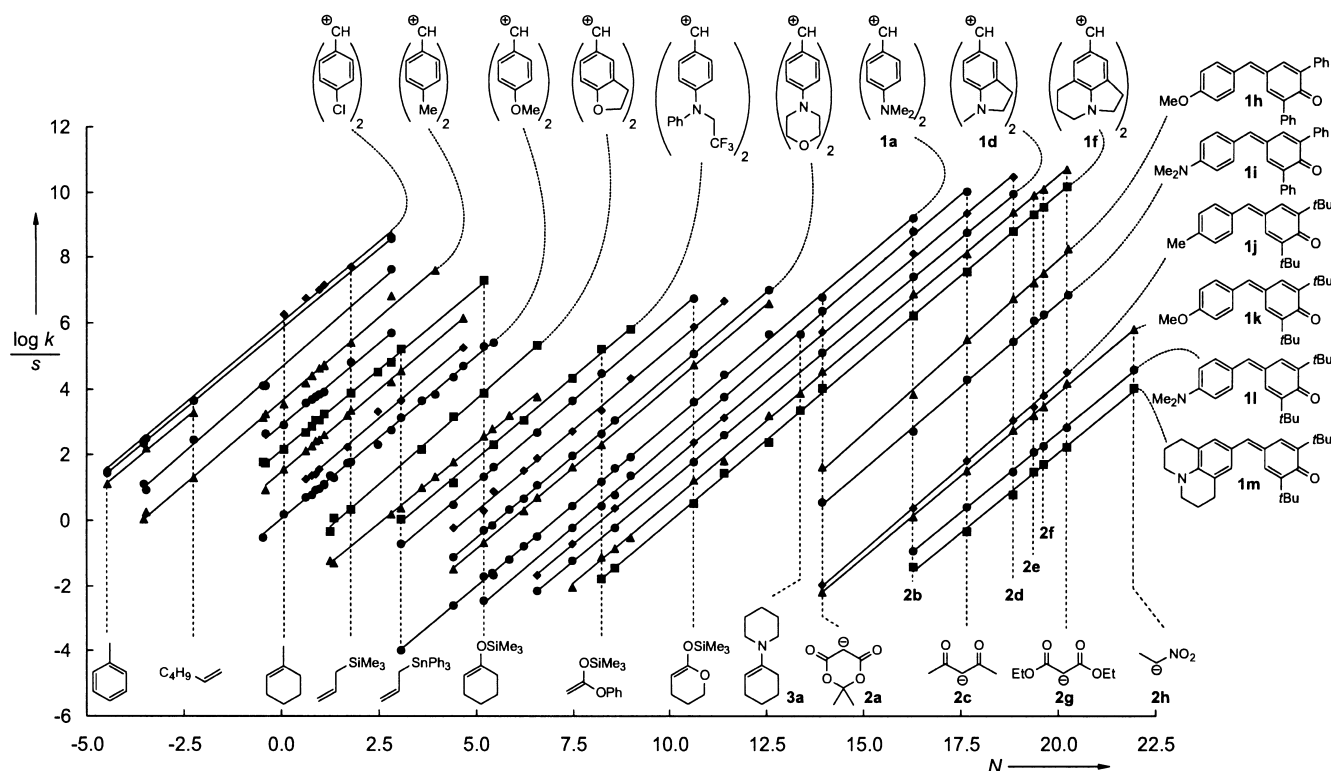


Figure 1. Plot of  $(\log k)/s$  versus the nucleophilicity parameter  $N$  for the reactions of benzhydryl cations and quinone methides with  $\pi$  nucleophiles and carbanions (correlation line for **1g** not depicted).

reactions of neutral nucleophiles with neutral electrophiles that undergo a large change in dipole moment and therefore show a larger solvent dependence<sup>[12]</sup> than the reactions of quinone methides with enamines.

Previous work has demonstrated that the  $N$  and  $s$  parameters of neutral  $\pi$  nucleophiles derived from their reactions with benzhydryl cations are widely applicable and also hold for the reactions of  $\pi$  nucleophiles with other types of carbocations, cationic metal  $\pi$  complexes, and diazonium ions.<sup>[2]</sup> Analogously, Lemek found that the reactivity parameters for the carbanions reported herein also hold for their reactions with typical Michael acceptors, for example, benzylidene malononitriles or benzylidene malonic esters.<sup>[13a]</sup> The accuracy of the predictions from Equation (1) decreases when benzhydryl cations are replaced by other types of electrophiles, because the steric situation around the electrophilic reaction centers is not any longer constant. However, the deviations are so moderate<sup>[14]</sup> that a comprehensive representation of electrophile–nucleophile combinations becomes possible with Equation (1).

In Figure 2, the nucleophiles are ordered in increasing reactivity from left to right, and electrophiles are ordered in increasing reactivity from top to bottom. In this arrangement, the diagonal line identifies electrophile–nucleophile combinations that proceed with a rate constant of  $1 \text{ L mol}^{-1} \text{ s}^{-1}$  at  $20^\circ \text{C}$  ( $E + N = 0$ ). Three domains are differentiated with color; the diffuse borders are partially a result of the variable magnitude of  $s$ . The blue sector (cold) identifies combinations of electrophiles with nucleophiles that are too slow to occur at room temperature, whereas red (hot) indicates diffusion-controlled reactions with rate constants of  $10^9$ –

$10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$ . Reactions that have rate constants between  $10^{-6}$  and  $10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$  are found in the green and yellow zones. When moving from left to right or from top to bottom in the green zone, the increase in reactivity is predominately a

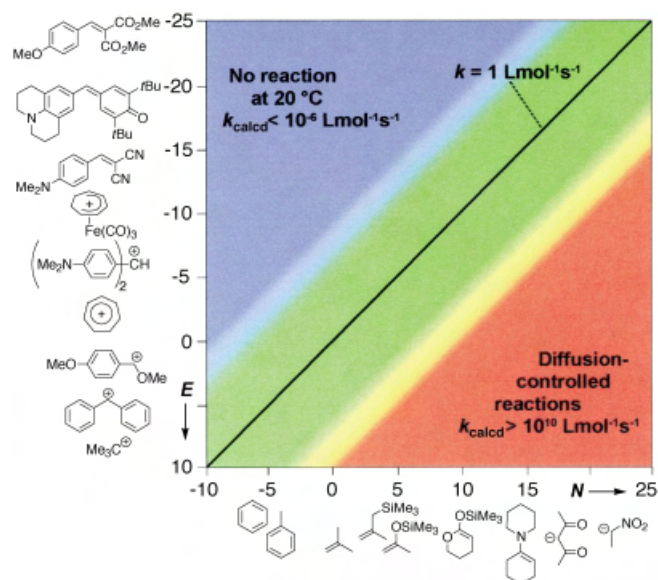


Figure 2. From inertness to diffusion control: a semiquantitative model of polar organic reactivity.

result of a decrease in  $\Delta H^\ddagger$ ,<sup>[15b]</sup> which becomes zero in the yellow strip. The yellow domain encompasses reactions that are not diffusion controlled with  $\Delta H^\ddagger = 0$  (entropy-controlled reactions).<sup>[15]</sup>

Equation (1), which was previously used to describe the rate constants for the reactions of carbocations with neutral nucleophiles,<sup>[2]</sup> has now also been demonstrated to hold for reactions of carbocations with carbanions and for reactions of carbanions with neutral electrophiles. It thus became possible to combine the chemistry of carbocations with that of carbanions, and to construct electrophilicity and nucleophilicity scales that cover almost 30 orders of magnitude.

A three-parameter equation that neglects steric effects can certainly not be expected to provide accurate rate constants. However, it has been shown for reactions of carbocations with  $\pi$  nucleophiles that the deviation between calculated and experimental rate constants seldom exceeds a factor of 30 when bulky reagents are excluded<sup>[14]</sup>—a remarkable agreement in view of the many orders of magnitude covered by this model. Since this precision is sufficient for planning organic syntheses, a common set of reactivity parameters  $E$ ,  $N$ , and  $s$  can be used to describe reactions as different as Friedel–Crafts alkylations,<sup>[16]</sup> Hosomi–Sakurai allylations,<sup>[17]</sup> Nicholas propargylations,<sup>[18]</sup> Mukaiyama aldol reactions,<sup>[19]</sup> Mannich aminoalkylations,<sup>[20]</sup> azo couplings,<sup>[21]</sup> palladium-catalyzed allylations,<sup>[22]</sup> Michael additions,<sup>[23]</sup> and many others. Multi-center reactions, including  $S_N2$ -type reactions, are excluded.

This model does not only allow one to determine whether a certain reaction is likely to take place, but also identifies diffusion-controlled reactions of reactive intermediates, which may be associated with a breakdown of regio- and stereo-selectivity.<sup>[24]</sup> Whereas small differences between  $k$  and  $k_{\text{calcd}}$  from Equation (1) cannot be interpreted, deviations of several orders of magnitude have mechanistic significance. A common feature of the reactions that follow Equation (1) is the formation of one new single bond in the rate-determining step. Strong deviations may therefore indicate an alternative reaction mechanism or be a result of special stabilizing or destabilizing interactions in the transition states, as expected from Pearson's hard and soft acids and bases principle.<sup>[25]</sup>

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# Rate Acceleration through Dispersion Interactions: Effect of a Hemicarcerand on the Transition State of Inner Phase Decompositions of Diazirines\*\*

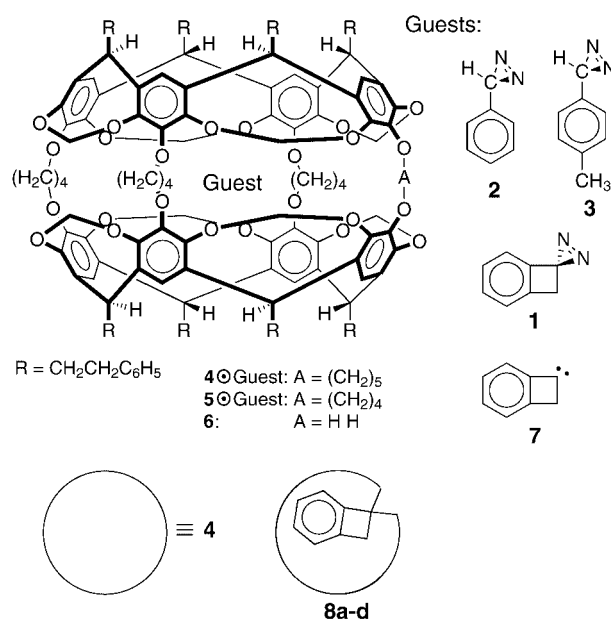
Ralf Warmuth,\* Jean-Luc Kerdelhué, Sigifredo Sánchez Carrera, Kevin J. Langenwalter, and Neil Brown

In memory of Donald J. Cram

The concept of molecular container compounds and of single molecule incarceration has provided a novel way to address topics that are important to chemical and biological sciences,<sup>[1]</sup> such as reactive intermediates,<sup>[2–5]</sup> through-space phenomena,<sup>[6]</sup> templating,<sup>[7]</sup> stereoisomerism,<sup>[8]</sup> and catalysis.<sup>[9]</sup> In addition, the investigation of inner phase reactions allows one to probe the effect of a constrained, electron-rich environment on the transition states of a reaction.<sup>[10]</sup> Insight gained from such studies is expected to be very important for the design of novel catalysts and for the understanding of the stabilization of the transition state in enzyme-catalyzed reactions.<sup>[11]</sup> Recently, Rebek and co-workers demonstrated that bimolecular reactions can be strongly accelerated in the presence of a self-assembled molecular capsule.<sup>[9]</sup> The observed acceleration of Diels–Alder reactions was explained by the increased apparent concentration in the tetrameric ene–diene–capsule complex. Whether molecular containers can, like enzymes, stabilize transition states, and if so, which interactions play a role, still remains to be established.

Here, we show for the first time that inner phase reactions, such as the thermal decomposition of diazirines, can be strongly accelerated through dispersion interactions between the hemicarcerand shell and the transition state.

Our investigation of the thermal decomposition of aryldiazirines **1–3** in the inner phase of hemicarcerands **4**<sup>[12]</sup> and **5**<sup>[13]</sup> was initiated by an unexpected observation. The reaction of **6** with 1,5-pentandiol di-*p*-tosylate and Cs<sub>2</sub>CO<sub>3</sub> in hexamethylphosphoramide (HMPA) in the presence of excess **1**,<sup>[14b]</sup> unexpectedly did not afford the hemicarceplex **4** ⊙ **1**; instead only four isomeric products **8a–d** were isolated, which evidently result from an intramolecular addition of **7** to an arene unit of the host **4**.<sup>[15]</sup> Thus within the reaction time (24–48 h), **1** must have decomposed thermally in the inner phase of **4**,<sup>[16]</sup> which is very surprising in light of the much higher thermal stability of neat **1**. Shortening of the reaction time



(2 h) gave a small amount of a new hemicarceplex (27%) in addition to **8a–d** (10%). The same hemicarceplex is formed in 80% yield if a solution of **4** and excess **1** in CDCl<sub>2</sub>CDCl<sub>2</sub> ([D<sub>2</sub>]TCE; TCE = 1,1,2,2-tetrachloroethane) is stirred for 50 min at 0 °C (Figure 1 a).<sup>[17]</sup>

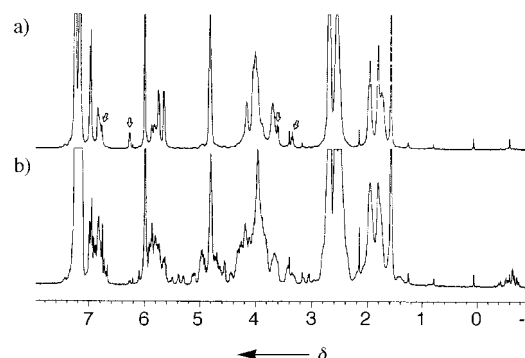


Figure 1. <sup>1</sup>H NMR spectra (400 MHz, 24 °C) of a) of **4** ⊙ **1** (80%) in [D<sub>2</sub>]TCE and b) same solution as (a) after 16 h at 24 °C. Signals assigned to the protons of incarcerated **1** are marked with arrows.

We assign this new hemicarceplex to **4** ⊙ **1** based on the following features and observations. 1) The FAB mass spectrum shows signals for [*M*<sup>+</sup>+1] at *m/z* 2393 (54%), and for [*M*<sup>+</sup>–1+1] at *m/z* 2263 (100%). 2) Brief irradiation (λ > 350 nm) completely decomposes the complex leading to the formation of **8a–d**. 3) In CDCl<sub>3</sub>, the hemicarceplex decomposes within a few hours by the thermolysis of the guest (36%) and by decomplexation (64%) leading to **4** ⊙ CDCl<sub>3</sub><sup>[12]</sup> and free **1**. In [D<sub>2</sub>]TCE, the dissociation of the hemicarceplex is almost completely suppressed, and **8a–d** are formed in about 90% yield (Figure 1 b). 4) If **1** is thermolyzed in the presence of **4** ⊙ TCE<sup>[12]</sup> neither the addition products **8a–d** are formed nor is the decomposition rate of **1** affected. 5) The <sup>1</sup>H NMR spectrum displays signals at δ = 6.89 (t, 1 H), 6.36 (d, 1 H), 3.62 (d, 1 H), 3.43 (t, 1 H), and 2.73 (s, 2 H), which

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

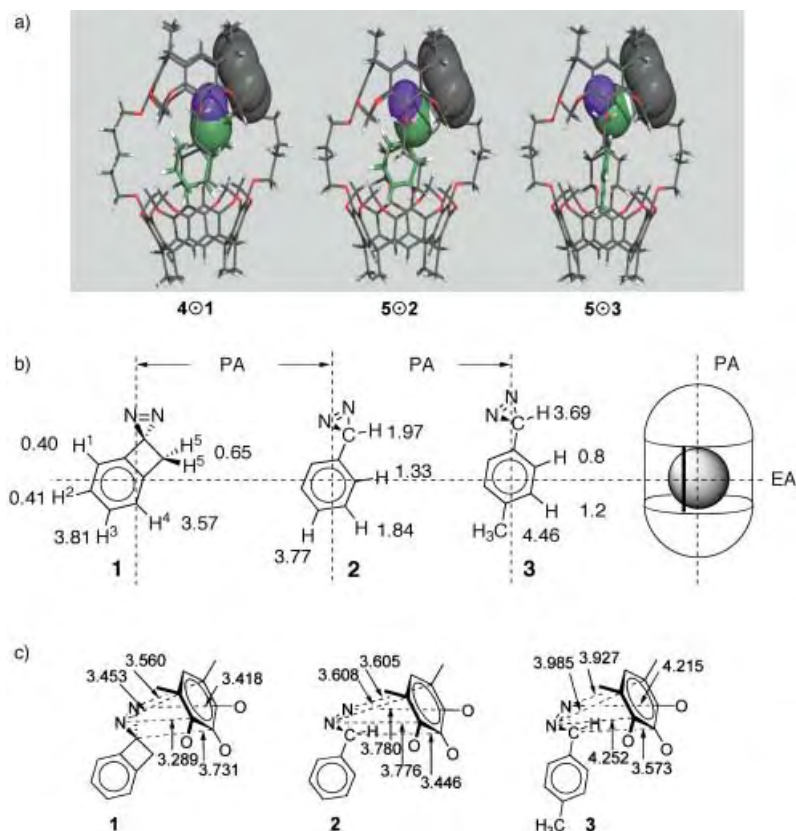


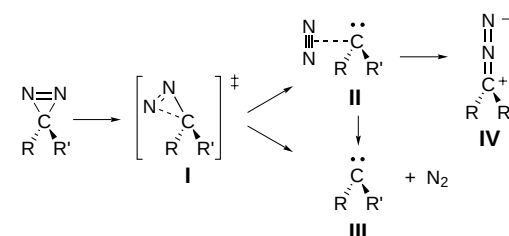
Figure 2. a) MM2 energy-minimized structures of **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. Color code: O: red; H: white; N: blue; host C: gray; guest C: green. b) Hemicarcerand-induced upfield shifts (in ppm) of guest proton resonances in **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. Guests **1**–**3** are shown in their preferred inner phase orientation with respect to the polar axis and the equatorially located axis of **4** and **5**. c) Calculated (MM2) atom–atom distances [in Å] between **1**–**3** and the host's arene unit that is facing the diazirine ring in **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. PA = polar axis; EA = equatorial axis.

are assigned to the protons H2, H1, H4, H3, and H5 of incarcerated **1**, respectively (Figure 2b and Supporting Information). All this strongly supports that the new hemicarceplex is **4** ⊙ **1** and that **8a–d** are formed through an inner phase decomposition of **1**.

To quantify the effect of the hemicarcerand on the thermal stability of aryldiazirines, we measured the thermal decomposition rates of **4** ⊙ **1**, **5** ⊙ **2**,<sup>[5a,b]</sup> and **5** ⊙ **3** as well as of free **1**, **2**, and **3** at different temperatures. Arrhenius plots provided activation energies  $E_a$  and preexponential factors  $\ln A$  from which  $\Delta G^\ddagger$ ,  $\Delta H^\ddagger$ , and  $T\Delta S^\ddagger$  were calculated (Table 1 and

Supporting Information). Remarkably, whereas **2** and **3** decompose as fast or slightly slower in the inner phase than in the bulk, the decomposition of **1** is 15-fold faster in the inner phase of **4**. An analysis of the activation parameters shows that this effect is enthalpic in nature.<sup>[18]</sup> Polarity effects cannot account for the large difference in the ratio between inner phase and bulk phase rates  $k_{IP}/k_{BP}$  (Table 1), since decomposition rates for diazirines are essentially insensitive to the solvent polarity.<sup>[19, 20]</sup>

Kinetic studies and ab initio calculations of the thermolysis of diazirines predict a  $C_1$ -symmetric diazirine-like transition state **I** with differently elongated C–N bonds which leads either to free carbene **III** or a carbene–nitrogen encounter complex **II**.<sup>[21, 22]</sup> The latter further reacts to **III** and/or diazomethane **IV** depending on the substituents R, R', and the medium (Scheme 1).<sup>[21]</sup>



Scheme 1. Possible reaction channels for the decomposition of diazirines.

From the measured hemicarcerand-induced upfield shifts of the guest proton resonances we deduce preferred guest orientations (Figure 2b) in which all diazirine groups are located inside a polar cap of **4** or **5**. These orientations compare well with those obtained from force field calculations (Figure 2a).<sup>[23, 24]</sup> Thus, the increased thermal stability of **3** upon incarceration could be a result of a small steric effect as **3** approaches the transition state **I**. This is consistent with the unchanged stability of the less cavity-filling **2** and the increase in the number of van der Waals contacts (in parentheses) between the diazirine group and the arene groups of the hemicarcerand, which increase in the order **5** ⊙ **3** (16) ≫ **5** ⊙ **2** (3) > **4** ⊙ **1** (1). However, steric effects cannot explain the accelerated de-

Table 1. Activation parameters ( $E_a$ ,  $\ln A$ ,  $\Delta G^\ddagger$ ) for the thermal decomposition of **1**–**3**, **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**.<sup>[a]</sup>

|                                             | <b>1</b> <sup>[b]</sup><br>TCE <sup>[d]</sup> | <b>4</b> ⊙ <b>1</b> <sup>[c]</sup><br>TCE | <b>2</b> <sup>[b]</sup><br>TCE <sup>[d]</sup> | <b>5</b> ⊙ <b>2</b> <sup>[c]</sup><br>TCE | <b>3</b> <sup>[b]</sup><br>TCE <sup>[d]</sup> | <b>5</b> ⊙ <b>3</b> <sup>[c]</sup><br>TCE | <b>5</b> ⊙ <b>3</b> <sup>[c]</sup><br>THF |
|---------------------------------------------|-----------------------------------------------|-------------------------------------------|-----------------------------------------------|-------------------------------------------|-----------------------------------------------|-------------------------------------------|-------------------------------------------|
| $E_a$                                       | 26.4 ± 0.2                                    | 24.5 ± 0.8                                | 30.7 ± 0.5                                    | 27.4 ± 0.3                                | 29.8 ± 0.2                                    | 27.4 ± 0.3                                | 28.3 ± 0.4                                |
| $\ln A$                                     | 31.8 ± 0.3                                    | 31.4 ± 1.2                                | 35.5 ± 0.7                                    | 30.9 ± 0.5                                | 35.0 ± 0.2                                    | 30.6 ± 0.4                                | 31.7 ± 0.6                                |
| $\Delta G^\ddagger$                         | 25.0 ± 0.2 <sup>[e]</sup>                     | 23.3 ± 1.1 <sup>[e]</sup>                 | 26.6 ± 0.7 <sup>[f]</sup>                     | 26.5 ± 0.5 <sup>[f]</sup>                 | 26.1 ± 0.2 <sup>[f]</sup>                     | 26.7 ± 0.4 <sup>[f]</sup>                 | 26.9 ± 0.5 <sup>[f]</sup>                 |
| $\Delta\Delta H^\ddagger$ <sup>[g]</sup>    |                                               | 1.9                                       |                                               | 3.3                                       |                                               | 2.4                                       | 1.5                                       |
| $\Delta(T\Delta S^\ddagger)$ <sup>[g]</sup> |                                               | 0.2                                       |                                               | 3.2                                       |                                               | 3.0                                       | 2.3                                       |
| $\Delta\Delta G^\ddagger$ <sup>[g]</sup>    |                                               | 1.7                                       |                                               | 0.1                                       |                                               | −0.6                                      | −0.8                                      |
| $k_{IP}/k_{BP}$ <sup>[h]</sup>              |                                               | 15/1                                      |                                               | 1.2/1                                     |                                               | 1/2.4                                     | 1/3.2                                     |

[a] Standard errors were estimated by linear least-squares regression of Arrhenius plots. All energy values are in kcal mol<sup>−1</sup>. [b] Determined by UV/Vis spectroscopy. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Contained 5% CH<sub>3</sub>COOH as carbene and diazomethane trap. [e]  $T = 313$  K. [f]  $T = 345$  K. [g]  $\Delta\Delta X^\ddagger = \Delta X^\ddagger(\text{free guest}) - \Delta X^\ddagger(\text{incarcerated guest})$ . [h]  $k_{IP}$  = inner phase rate constant;  $k_{BP}$  = bulk phase rate constant.



composition of **1**. We propose that dispersion forces strongly stabilize the transition state for the decomposition of **1**. The inner phases of **4** and **5** are lined with eight electron-rich, highly polarizable arene groups. The elongated C–N bonds of the transition state **1** are more polarizable than the intact bonds in the ground state and are able to interact strongly with the host's arene units through dispersion forces. Earlier, Dougherty et al. showed the importance of dispersion interactions in biomimetic catalysis.<sup>[25]</sup>

In all three hemicarceplexes, the breaking C–N bonds will be located in close proximity to a highly polarizable arene unit of **4** and **5**, suitable for stabilization of the transition state through dispersion interactions. In agreement with this, the decomposition rate of free **1** slightly increases with increasing bulk phase polarizability (see Supporting Information).<sup>[20]</sup>

A reason why only the thermolysis of **1** but not that of **2** and **3** is strongly accelerated through London forces might lie in the different distances between the diazirine ring and the arene ring (shown as space-filling representation in Figure 2a), that is closest to and almost coplanar with it. The distances between the atoms of the diazirine ring and the O-substituted carbon atoms of the host's arene ring decrease in the order  $5 \odot 3 \gg 5 \odot 2 > 4 \odot 1$  (Figure 2c) which is opposite to the observed stabilization of the transition state ( $5 \odot 3 < 5 \odot 2 \ll 4 \odot 1$ ) and consistent with the strong distance dependence ( $\propto R^{-6}$ ) of dispersion interactions.<sup>[26]</sup> Further insight into the specific interactions between host and transition state should come from QM/MM calculations, which are currently in progress.

In conclusion, our investigations show that inner phase reaction rates can be strongly altered through the interplay of rate-accelerating dispersion interactions between the transition state and the highly polarizable arene units of the surrounding hemicarcerand and steric effects due to the constrained environment. This suggests that even larger rate enhancements are possible for reactions with very negative activation volumes, such as Diels–Alder reactions or Cope and Claisen rearrangements.<sup>[27]</sup> Moreover, our studies indicate that properly aligned tryptophan or tyrosine side chains in the active site of an enzyme might account for a stabilization of the transition state by up to 1–2 kcal mol<sup>−1</sup> per formed or broken bond in an enzyme-catalyzed reaction.<sup>[11a]</sup>

## Experimental Section

**5**  $\odot$  **3**: *p*-Tolyldiazirine **3** (0.110 mL) was added by syringe to a suspension of **6** (150 mg, 0.068 mmol), 1,4-butanediol dimesylate (130 mg, 0.53 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (700 mg) in dry HMPA (8 mL). The suspension was stirred for four days under argon in the dark at room temperature. The reaction was quenched by the addition of brine (40 mL). The precipitate was filtered off, washed with water (2  $\times$  10 mL) and methanol (2  $\times$  10 mL), and dried at high vacuum. The crude product was dissolved in the minimum amount of chloroform and purified by column chromatography (silica gel, chloroform). Concentration of the product fraction gave **5**  $\odot$  **3** (54 mg, 33 % yield) as a white powder.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 24 °C):  $\delta$  = 7.27–7.12 (m, 40H), 6.89 (s, 4H; aryl-*H*), 6.77 (s, 4H; aryl-*H*), 5.98, 5.94 (AB system, <sup>3</sup>J<sub>A,B</sub>(H,H) = 8 Hz, 4H; aryl-*H*, **3**), 5.71 (d, <sup>3</sup>J(H,H) = 6.8 Hz, 4H; OCH<sub>outer</sub>HO), 5.66 (d, <sup>3</sup>J(H,H) = 6.8 Hz, 4H; OCH<sub>outer</sub>HO), 4.89 (t, <sup>3</sup>J(H,H) = 7.6 Hz, 4H; CH<sub>methine</sub>), 4.88 (t, <sup>3</sup>J(H,H) = 7.6 Hz, 4H; CH<sub>methine</sub>), 4.36 (d, <sup>3</sup>J(H,H) = 6.8 Hz, 4H; OCH<sub>inner</sub>HO), 4.10 (d, <sup>3</sup>J(H,H) = 6.8 Hz, 4H; OCH<sub>inner</sub>HO), 3.97 (brs, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.88 (brs, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 2.76–2.63 (m, 16H), 2.56–2.42

(m, 16H; 1.84 (brs, 16H), –1.68 (s, 1H; CH<sub>methine</sub>, **3**) –2.12 (s, 3H; CH<sub>3</sub>, **3**); LR FAB-MS (NBA matrix): *m/z*: 2383 (100) [*M*<sup>+</sup>+2], 2354 (78) [*M*<sup>+</sup> – N<sub>2</sub>+1], 2351 (56) [*M*<sup>+</sup> – 3+2]; C,H,N analysis calcd (%) for C<sub>152</sub>H<sub>144</sub>N<sub>2</sub>O<sub>24</sub>: C 76.62, H 6.09, N 1.18; found: C 76.49, H 5.91, N 0.95.

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## Supramolecular Cluster Catalysis: Benzene Hydrogenation Catalyzed by a Cationic Triruthenium Cluster under Biphasic Conditions\*\*

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*Dedicated to Professor Lord Lewis of Newnham*

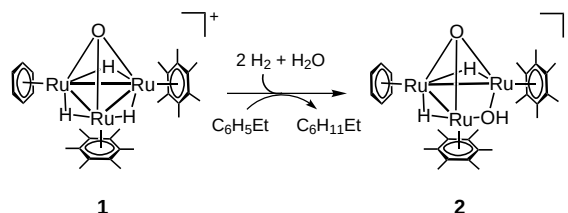
Organometallic catalysis most often proceeds through a catalytic cycle that involves the coordination of the substrate, either by ligand substitution or by oxidative addition, transformation of the coordinated substrate, and liberation of the product, either by decooordination or by reductive elimination.<sup>[1]</sup> Classical examples that have been studied in great detail are the hydrogenation of olefins with Wilkinson's catalyst<sup>[2]</sup> and the carbonylation of methanol with rhodium iodide (Monsanto Process).<sup>[3]</sup> The complete characterization of the intermediates of the latter process and the proposal of a well-established catalytic cycle represents one of the triumphs of organometallic chemistry.<sup>[4]</sup>

In all these reactions, the elementary steps of the catalytic process are believed to occur within the first coordination sphere of the organometallic catalyst.<sup>[5]</sup> We now have reasons to believe that organometallic catalysts may transform a substrate without prior coordination, the interactions between both partners entirely relying on weak intermolecular contacts. Although hydrogen transfer from a catalyst molecule to a substrate via a merely hydrogen-bonded catalyst–substrate complex has already been considered as the mechanism of ketone transfer hydrogenation reactions,<sup>[6]</sup> catalytic transformations by host–guest interactions and molecular recognition are generally accepted only in enzymatic catalysis.<sup>[7]</sup>

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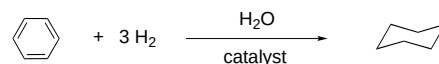
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The water-soluble organometallic cluster cation **1** (see Scheme 1), accessible from  $[(\eta^6\text{-C}_6\text{H}_6)\text{Ru}(\text{H}_2\text{O})_3]^{2+}$  with  $[(\eta^6\text{-C}_6\text{Me}_6)_2\text{Ru}_2(\mu_2\text{-H})_3]^+$  in aqueous solution and isolated as the  $\text{BF}_4^-$  salt,<sup>[8]</sup> was found to catalyze the hydrogenation of aromatic substrates under biphasic conditions. An unusually high catalytic activity of **1** was observed for the hydrogenation of ethylbenzene. From the reaction mixture the cluster cation **2** could be isolated as the  $\text{BF}_4^-$  salt (Scheme 1).<sup>[9]</sup>



Scheme 1. Hydrolysis of the closed cluster cation **1** to give the open cluster cation **2** during the hydrogenation of ethylbenzene to ethylcyclohexane under biphasic conditions (no free  $\text{C}_6\text{H}_{12}$  or  $\text{C}_6\text{Me}_6$  detected).

Cation **2**, dissolved in water, catalyzes the hydrogenation of aromatic compounds with higher activity than cation **1**: The reaction proceeds with a catalyst/substrate ratio of 1/1000 under hydrogen pressure (60 bar) at  $110^\circ\text{C}$  with vigorous stirring of the biphasic system. For benzene, the reaction is almost complete within 15 min, the catalytic turnover number (TON) being 911, corresponding to a catalytic turnover frequency (TOF) of  $3644\text{ h}^{-1}$ . Cation **2** can be recovered unaltered as the  $\text{BF}_4^-$  salt after a catalytic run from the aqueous phase and reused. Under identical conditions, cation **1** catalyzes the hydrogenation of benzene with a TOF of  $289\text{ h}^{-1}$  (Scheme 2).



Scheme 2. Hydrogenation of benzene to cyclohexane catalyzed by **1**- $\text{BF}_4$  or by **2**- $\text{BF}_4$  (catalyst/substrate 1:1000, 60 bar  $\text{H}_2$ ,  $110^\circ\text{C}$ ) in water (TOF  $289\text{ h}^{-1}$  for **1** and  $3544\text{ h}^{-1}$  for **2**, respectively).

Although a large number of organometallic complexes are known to catalyze the hydrogenation of olefins or acetylenes, only very few complexes are reported to catalyze the hydrogenation of aromatic compounds (TOF given in parentheses):  $[(\eta^6\text{-C}_6\text{Me}_6)_2\text{Ru}_2(\mu_2\text{-H})(\mu_2\text{-Cl})_2]\text{Cl}_2$  ( $241\text{ h}^{-1}$ ),<sup>[10]</sup>  $[(\eta^5\text{-C}_5\text{Me}_5)_2\text{Rh}_2(\mu_2\text{-Cl})_2]$  ( $11\text{ h}^{-1}$ ),<sup>[11]</sup>  $[(\eta^3\text{-C}_3\text{H}_5)_3\text{Co}(\text{P}(\text{OMe})_3)_3]$  ( $0.7\text{ h}^{-1}$ ),<sup>[12]</sup>  $[\text{RuH}_2(\eta^2\text{-H}_2)_2(\text{PCy}_3)_2]$  ( $1.6\text{ h}^{-1}$ ),<sup>[13]</sup>  $[\text{Nb}(\text{OC}_6\text{-HPh}_4\text{-2,3,5,6})_2\text{Cl}_3]$  in combination (1:3) with  $\text{BuLi}$  ( $409\text{ h}^{-1}$ ),<sup>[14]</sup>  $[(\eta^6\text{-C}_6\text{H}_6)_4\text{Ru}_4(\mu_3\text{-H})_4]\text{Cl}_2$  in water ( $376\text{ h}^{-1}$ )<sup>[15]</sup> or in ionic liquids ( $364\text{ h}^{-1}$ ),<sup>[16]</sup> and  $[(\eta^6\text{-C}_6\text{H}_6)_2\text{Ru}_2(\mu_2\text{-Cl}_2)\text{Cl}_2]$  ( $1998\text{ h}^{-1}$ ) in water.<sup>[17]</sup> The hydrogenation of arenes falls in general within the domain of heterogeneous catalysis: Millions of tons of benzene are hydrogenated per year to give cyclohexane using Raney nickel as the heterogeneous catalyst; the so-called IFP (Institut Français du Pétrole) process<sup>[18]</sup> using nickel and cobalt salts in combination with triethylaluminum seems destined to take over.<sup>[19]</sup>

In the case of **2**, catalyzing the hydrogenation of ethylbenzene, no substitution of a  $\eta^6$ -bonded arene ligand (benzene or hexamethylbenzene) in **2** by ethylbenzene is observed. The recovered material shows the identical  $^1\text{H}$  NMR spectrum and the same catalytic activity for further catalytic runs as the original **2**-BF<sub>4</sub>. This striking observation rules out the conventional organometallic mechanism for the catalytic hydrogenation of aromatic substrates by **2**, in which the substrate is coordinated to the metal of the active complex, because in this case one of the three arene ligands (either benzene or hexamethylbenzene) in **2** should be replaced by ethylbenzene. We therefore conclude that the aromatic substrate molecule is not coordinated to ruthenium throughout the catalytic cycle but interacts with the Ru<sub>3</sub> surface in **2** only through weak intermolecular interactions. This may be possible thanks to the three  $\eta^6$ -arene ligands in **2** which form a hydrophobic pocket capable of accommodating the aromatic substrate and in placing it in a perfect position underneath the Ru<sub>3</sub> face opposite to the oxo cap of the cluster. In the spirit of the triterpene cyclases<sup>[7]</sup> and due to the lipophilic character of both substrate and catalyst binding pocket, the host–guest interaction is very favorable, as the aromatic substrate tries to escape from the aqueous medium.

To verify this hypothesis, we carried out a mass spectrometric study of mixtures of hexadeuterobenzene with **1** and with **2** (as BF<sub>4</sub><sup>−</sup> salts) in acetone. The adducts C<sub>6</sub>D<sub>6</sub> ⊂ **1** and C<sub>6</sub>D<sub>6</sub> ⊂ **2** · H<sub>2</sub>O can be clearly identified in the electrospray mass spectrum. The intensity of these peaks, which can be assigned unambiguously on the basis of their characteristic Ru<sub>3</sub> isotope pattern, increases with the concentration of C<sub>6</sub>D<sub>6</sub> in the acetone solution. These results strongly support the hypothesis of host–guest interactions between the substrate and the catalyst.

Facial coordination of an arene on the triangular face of a cluster has been known since the characterization of [Os<sub>3</sub>(CO)<sub>9</sub>(μ<sub>3</sub>-η<sup>2</sup>:η<sup>2</sup>:η<sup>2</sup>-C<sub>6</sub>H<sub>6</sub>)] by Lewis et al.<sup>[20]</sup> These structures have been invoked as models for the chemisorption of arene derivatives at a threefold site of close-packed metal surfaces. Incorporating arene derivatives as ancillary ligands constitutes a good model for the interaction between a hydrophobic triangular face and an arene derivative. A search of the Cambridge Structural Database reveals eleven such structures composed of three {(η<sup>5</sup>-C<sub>5</sub>R<sub>5</sub>)M} moieties capped by an arene, yielding [(η<sup>5</sup>-C<sub>5</sub>R<sub>5</sub>)<sub>3</sub>M<sub>3</sub>(μ<sub>3</sub>-η<sup>2</sup>:η<sup>2</sup>:η<sup>2</sup>-arene)]<sup>n+</sup> (M = Co, Ru, Rh, R = H, Me; Figure 1a).<sup>[21]</sup> Comparing these structures to the molecular structure of clusters **1** and **2** (Figure 1b) suggests that these are preorganized to accommodate a benzene host. However, it should be emphasized that all three ruthenium centers in clusters **1** and **2** are coordinatively saturated and thus cannot interact through dative bonds with the arene host. The host–guest interaction must rely solely on weak hydrophobic and van der Waals contacts. Moreover, the bridging hydrides and hydroxide shield the access of the guest to the metal face.

In a modeling study,<sup>[22]</sup> a benzene molecule was docked in the hydrophobic pocket spanned by the three  $\eta^6$ -bonded arene ligands. Setting the {Ru<sub>3</sub>face}–benzene distance at 3.00 Å and minimizing the steric repulsion suggests that no major cluster reorganization is necessary to accommodate a

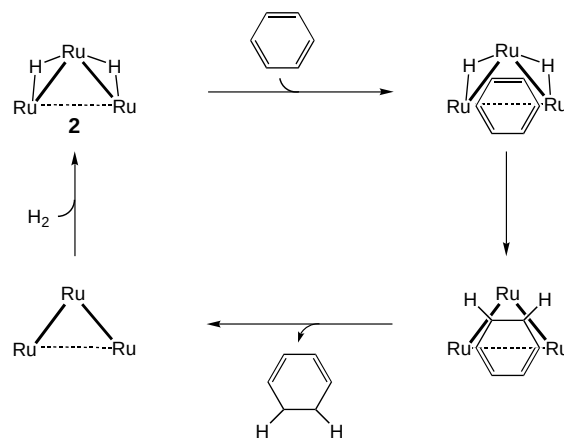


Figure 1. a) Superposition of the molecular structure of the eleven structurally characterized clusters [(η<sup>5</sup>-C<sub>5</sub>R<sub>5</sub>)<sub>3</sub>M<sub>3</sub>(μ<sub>3</sub>-η<sup>2</sup>:η<sup>2</sup>:η<sup>2</sup>-arene)]<sup>n+</sup> (M = Co, Ru, Rh); hydrogen atoms and arene substituents are omitted for clarity. b) Molecular structure of **2**, emphasizing the hydrophobic pocket and the preorganization to accommodate a benzene guest (compare with Figure 1a; C: green; H: white; Ru: magenta; O: red). c) CPK model of the optimized structure of C<sub>6</sub>H<sub>6</sub> ⊂ **2**; the [Ru]<sub>3</sub>-C<sub>6</sub>H<sub>6</sub> distance fixed at 3 Å,  $\eta^6$ -bound arenes green and white, docked benzene blue and white.

benzene host in the hydroxo-bridged cluster **2** (shortest H–H contact 1.60 Å; Figure 1c). With the catalytically less active cluster **1**, a similar procedure yields shorter H–H contacts (1.28 Å) in the energy-minimized structure, suggesting that the cluster must relax to accommodate the benzene guest.

We believe the hydrogenation of the aromatic substrate to occur within the hydrophobic pocket of the catalyst in a stepwise manner, that is to say via cyclohexadiene and cyclohexene intermediates. Thus, hydrogenation of the disubstituted *o*-, *m*-, and *p*-xylenes afford both *cis* and *trans* isomers of the corresponding dimethylcyclohexanes. This implies that after the dihydride transfer, the (partially) reduced substrate leaves the hydrophobic pocket, allowing regeneration of the active catalyst by H<sub>2</sub> oxidative addition. Accordingly, in the hydrogenation of benzene with **2**-BF<sub>4</sub> under biphasic conditions (catalyst/substrate ratio of 1/1000, H<sub>2</sub> 60 bar, 20 °C, 1 h), small amounts of 1,3-cyclohexadiene and of cyclohexene can indeed be detected by GC analysis. A mechanism consistent with these observations is outlined in Scheme 3.

The reaction of cyclohexene with D<sub>2</sub> catalyzed by **2**-BF<sub>4</sub> in H<sub>2</sub>O (catalyst/substrate ratio of 1/1000, D<sub>2</sub> 40 bar, 110 °C, 15 min) affords exclusively 1,2-dideuterocyclohexane, suggesting that the hydrogenation mechanism involves indeed a



Scheme 3. Proposed mechanism for the stepwise catalytic hydrogenation of benzene to cyclohexane (first step: benzene to 1,3-cyclohexadiene) with the intact cluster cation **2** (arene, oxo, and hydroxo ligands omitted for clarity).



dihydride transfer from the cluster to the unsaturated substrate rather than a monohydride transfer from the cluster followed by protonation from water.

The hypothesis of supramolecular catalysis is further supported by the striking substrate selectivity of these cluster catalysts: Indeed, only benzene and moderately hindered benzene derivatives (such as toluene, ethylbenzene, xylenes), are efficiently hydrogenated. As can be appreciated from Figure 1c, highly substituted benzene derivatives (e.g. tetra- and hexamethylbenzene) are too bulky to fit into the hydrophobic pocket of **1** and **2** and are thus not hydrogenated.

To rule out the possibility of catalysis by microparticles (colloids or nanoclusters), we carried out a mercury poisoning experiment.<sup>[23–25]</sup> Mercury is well known to poison heterogeneous catalysts by amalgam formation; catalytically active metal particles formed by degradation of molecular precursors will therefore be amalgamated, which causes a complete loss of the catalytic activity.<sup>[26]</sup> A solution of **2**-BF<sub>4</sub> in water, however, stirred with metallic mercury for 1 h prior to filtration, shows almost the same catalytic activity for benzene hydrogenation as before (TOF 3500 h<sup>-1</sup>). This experiment clearly suggests that intact Ru<sub>3</sub> clusters are the catalytically active species.

With **2**-BF<sub>4</sub> as the catalyst, benzene can even be hydrogenated at room temperature: Under biphasic conditions (water/benzene) and a hydrogen pressure of 60 bar, the conversion of benzene is 98% after 4 h (TON 980, TOF 245 h<sup>-1</sup>). No other catalyst is known to hydrogenate benzene under such mild conditions.

From an academic point of view, arene hydrogenation catalysts **1** and **2** are of interest as they seem to pave the way towards a shift in paradigm for cluster catalysis. Indeed, clusters are often regarded as molecular architectures that lie at the interface between homogeneous and heterogeneous systems. The catalytic systems described herein lie at the interface between homogeneous, heterogeneous, and enzymatic catalysis. From an industrial point of view, catalyst **2** may be of great interest as it is, to the best of our knowledge, the mildest and most efficient molecular arene hydrogenation catalyst reported to date. Furthermore, these catalysts are devoid of expensive ligands: they can be formally regarded as solubilized ruthenium ions, the ligands provided either by the solvents (arene or water-derived anions) or the gas (H<sub>2</sub>).

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- [22] The extensible systematic force field (ESFF) code was used to optimize the gas-phase geometry of the host–guest complexes [C<sub>6</sub>D<sub>6</sub> ⊂ **1**]<sup>+</sup> and [C<sub>6</sub>D<sub>6</sub> ⊂ **2**]<sup>+</sup>. Keeping the cluster geometry frozen, the benzene guest was gradually allowed to approach the open face of the cluster. The total energy was minimized by varying the orientation of the benzene with respect to the {Ru3-face}. See: S. Barlow, A. L. Rohl, S. Shi, C. M. Freeman, D. O'Hare, *J. Am. Chem. Soc.* **1996**, *118*, 7578.
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# Immobilized Highly Charged Colloidal Crystals: A New Route to Three-Dimensional Mesoscale Structured Materials\*\*

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Mesoscale-ordered macroporous materials have attracted great interest over the last few decades. With a three-dimensional periodic variation in the dielectric constant on a scale comparable to optical wavelengths, they have outstanding optical properties, in particular photonic bandgaps are possible which offer the possibility to manipulate and guide light.<sup>[1–5]</sup> Apart from their applications in optics, these materials can be designed for a variety of other applications, for instance for use in catalysis.<sup>[6, 7]</sup> Previous synthetic routes took advantage of the self-assembly of hard-sphere colloids or emulsions to prepare macroporous materials with spheroidal voids arranged in a three-dimensional periodic structure.<sup>[8–13]</sup>

Herein we present a new method for preparing metallic mesostructures that starts from highly charged polymer colloids. At low ionic strength these systems self-assemble to form liquidlike, glasslike, or crystalline structures,<sup>[14]</sup> which can be immobilized in a crosslinked polyacrylamide hydrogel.<sup>[15]</sup> These hydrogels can be applied as chemical sensors or as “entropic traps” for the separation of macromolecules.<sup>[16]</sup> Our experiments show that such hydrogels are also suitable templates for the preparation of mesoscale ordered metals.

Highly charged colloids allow, due to the repulsive interaction, interparticular distances that can easily be varied by the number density of colloidal particles. Accordingly, in highly charged colloidal crystals the lattice constant can simply be tuned by the concentration. According to DLVO theory (DLVO = Derjaguin–Landau–Verwey–Overbeek) charged colloids interact through a screened electrostatic or Yukawa potential that originates from charged surface groups.<sup>[17]</sup> The strength of the interaction is highly dependent on the ionic strength of the dispersion medium. Crystals formed by these colloids are therefore sensitive to ionic impurities in the dispersion medium. This and the fact that changes in temperature and mechanical stress can destroy the colloidal crystals limit the number of possible synthesis routes for the preparation of mesoscale ordered materials. The immobilization of highly charged polymer colloids provides a possibility to overcome these difficulties. In a crosslinked polyacrylamide hydrogel the particles are fixed in their positions, and crystals formed by charged spheres are no longer sensitive to impurities in the dispersion medium or to physical stress. Thus, further preparation steps with this system can be carried out in an aqueous solution with high ionic strength.

To synthesize immobilized colloidal crystals we prepared polymer colloids consisting of polybutylacrylate. The monomer butylacrylate is commercially available and its emulsion polymerization provides highly charged and monodisperse particles.<sup>[18]</sup> Dynamic light scattering (DLS) experiments on these particles show that they have an average diameter of 200.5 nm (Figure 1) and are monodisperse; the geometrical

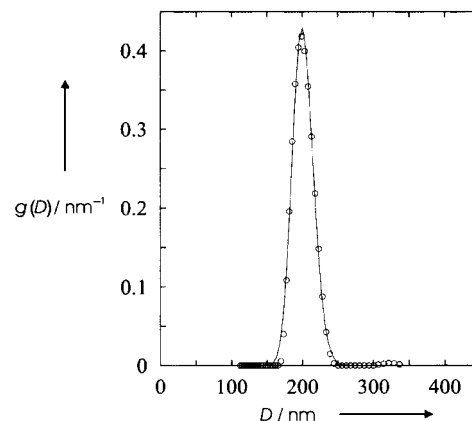


Figure 1. Size distribution  $g(D)$  of polybutylacrylate colloids measured by DLS. The measured values are fitted with a logarithmic normal distribution function. The fit gave a mean particle diameter  $D$  of 200.5 nm with a geometrical standard deviation of  $\sigma = 1.08$ .

standard deviation of the logarithmic normal distribution of their sizes amounts to only  $\sigma = 1.08$ . The particles have a zeta potential of  $-50$  mV in the pH range of 6 to 10 due to the dissociation of surface-bound acid groups. After removal of ions and other impurities from the dispersion, the spheres self-assemble into colloidal crystals and show opalescence when illuminated with light. The results of static light scattering experiments confirm the crystalline structure of the suspension, and by indexing the Bragg reflections a face-centered cubic (fcc) structure with a lattice constant of 1853 nm was determined.

In a subsequent step a sample with a high volume fraction of particles ( $\phi \approx 0.1$ ) was immobilized in a polyacrylamide hydrogel (Figure 2). The occurrence of Bragg reflections indicates that the order of the particles is maintained during the polymerization process. UV/Vis spectroscopy on these systems shows a shift of the absorption peak from 700 nm



Figure 2. Photograph of a crosslinked polyacrylamide hydrogel in which polybutylacrylate colloids are immobilized. The occurrence of Bragg diffraction of the incident visible light indicates long-range order of the particles.

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before to 830 nm after polymerization, which indicates an expansion of the lattice system during the polymerization process. These hydrogels with a periodic structure of the embedded polymer colloids then serve as a three-dimensional template for the synthesis of mesoscale structured silver.

Recently it has been shown that for hard-sphere systems the interspaces between colloidal particles can be filled electrochemically with another material.<sup>[19]</sup> To apply this technique to our systems, the hydrogel was polymerized directly onto the surface of a stainless steel electrode. By using this assembly as cathode, silver could be deposited into the interspaces by electrodeposition from an aqueous AgNO<sub>3</sub> solution. The resulting solid silver piece could easily be removed from the electrode surface; drying the sample at room temperature causes a slight shrinkage. The samples were then broken into pieces and were examined by scanning electron microscopy (SEM) without any further treatment.

The SEM images (Figures 3 and 4) reveal the three-dimensional structure of the silver/polybutylacrylate composite material. The latex spheres are arranged in hexagonal layers in which the particles do not touch each other but are

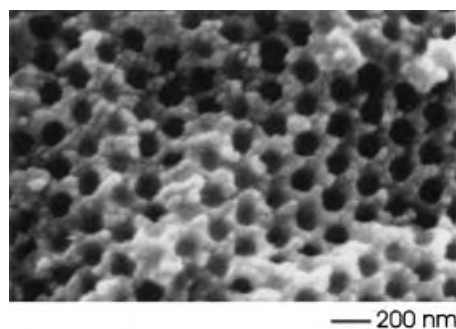


Figure 3. SEM image of the mesoscale structured silver sample. After the electrochemical silver deposition the periodic structure is maintained. The particle diameter of about 160 nm corresponds to the size determined by DLS if shrinkage of the particles during drying is considered.

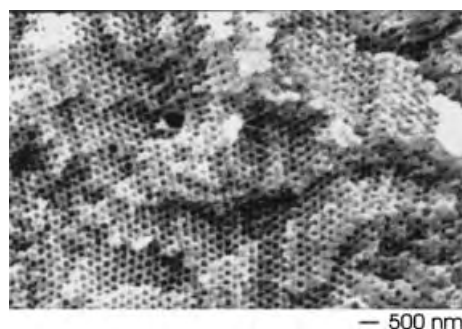


Figure 4. SEM image of larger areas of the silver sample shows the material's long-range ordered mesoscale structure. Monoparticular steps in the surface reveal the three-dimensional character of the periodic order (i.e. perpendicular to the plane of the picture).

separated by a silver layer with a well-defined thickness. The particles' diameter as determined from the SEM image is 160 nm, which differs from the value of 200 nm determined by dynamic light scattering due to shrinkage of the polymer spheres during drying. Although there are some defects in the structure, on the SEM image of larger regions of the sample

(Figure 4) the long-range order in the material can clearly be seen. Monoparticular steps in the surface reveal the three-dimensional character of the periodic order.

Similar samples starting from colloidal suspensions with lower particle number densities have been prepared. In these samples the particles do not exhibit long-range order after immobilization but are randomly distributed in the material. Evidently, at lower volume fraction the mean interparticle distance is too large and the crystalline structure is destroyed during polymerization.

In summary by using suspensions with high volume fractions ( $\phi \geq 0.1$ ) three-dimensional periodic structures have been prepared starting from highly charged colloidal crystals. This procedure is not limited to the electrodeposition of silver but can be extended to other materials, preferentially metals or alloys. For applications in optics the voids in these systems could be filled with semiconductor materials, which has been done already for hard-sphere systems.<sup>[19, 20]</sup> The adaption of this method to our systems is in progress. Thus, a novel route to photonic crystals is provided in which the lattice constant can be tuned by the volume fraction of colloidal particles. For use in catalysis a deposition of noble metals or other metals with catalytic activity can be considered. In this case the polymer spheres must be removed from the material after the deposition to create pores. As the size of the polymer colloidal particles can be adjusted over a wide range in the course of the emulsion polymerization, this procedure would lead to tailor-made catalyst surfaces with well-defined pore diameters and wall thicknesses.

### Experimental Section

**Colloidal suspension:** The suspension was prepared by emulsion polymerization at 80 °C using butylacrylate and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as initiator. The latex was purified by dialysis against distilled water and by subsequent treatment with ion-exchange resin.

**Hydrogels:** The hydrogels were prepared according to the method applied by Asher et al.<sup>[15]</sup> The colloidal suspension, acrylamide, crosslinker, and photoinitiator were mixed and shaken with ion-exchange resin. The mixture was injected into a cell between a quartz plate and a stainless steel electrode. The 1 mm thick layer was polymerized onto the electrode surface by using a UV lamp ( $\lambda = 366$  nm, 4 W) for 5 h.

**Electrodeposition:** Using the assembly of hydrogel and electrode as cathode it was possible to deposit silver electrochemically from a 0.5 M AgNO<sub>3</sub> solution into the interspaces between the colloidal particles. The deposition was carried out for 24 h at a current density of 1.5 mA cm<sup>-2</sup>.

**Zeta potential:** The zeta potential was measured with a Malvern Zetasizer model 3000 HSA.

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## The Rational Design of Anion Host Compounds: An Exercise in Subtle Energetics\*\*

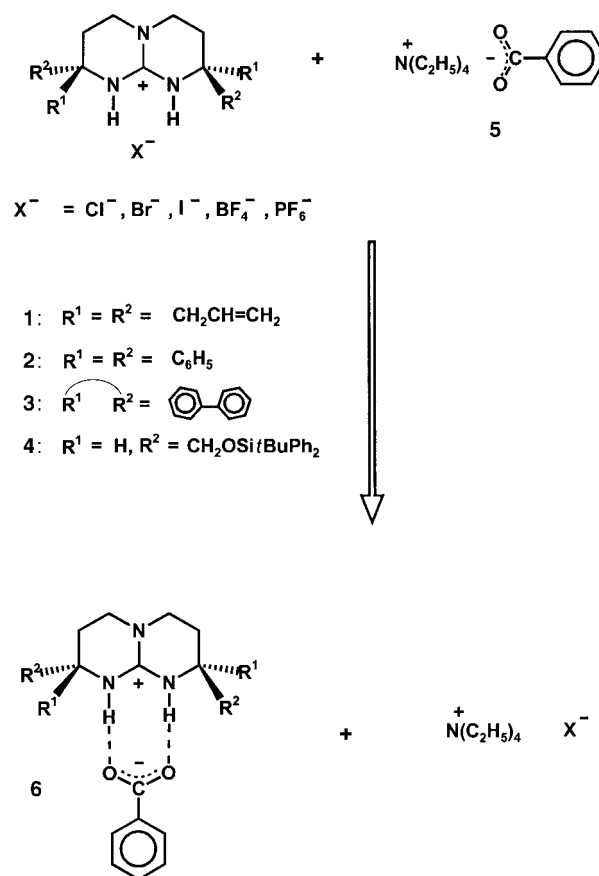
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For more than 100 years the lock-and-key metaphor of Emil Fischer served as the fundamental concept to comprehend molecular recognition interactions.<sup>[1]</sup> The central idea rests on the assumption that the mutual geometric fit of a pair of supramolecular binding partners dominates their thermodynamic affinity.<sup>[2]</sup> Thus, generations of synthetic chemists have strived to optimize the direct interaction mode of hosts towards a given guest species by subtle modification of their covalent structures taking the Gibbs energy of complex formation  $\Delta G^\circ$  and the equilibrium constant for association ( $K_{\text{ass}}$ ) as the ultimate judge. In many cases this approach did not live up to the expectations and met with only limited success. Here we describe an experimental attempt to evaluate the energetics of a simple host–guest system to develop more reliable guidelines for molecular recognition.

The failure of the lock-and-key model to rationalize general host–guest interactions can be traced to the premises of the

concept which focuses exclusively on the enthalpic interactions of just two interaction partners, neglecting the entropic components as well as all solvent contributions. The latter point in particular gives rise to the phenomenon of enthalpy–entropy compensation<sup>[3, 4]</sup> that accompanies all weak interactions in solution. The enthalpic gain on binding of host and guest can thus be counteracted by an entropic influence. As a consequence, the free energy of association  $\Delta G_{\text{ass}}^\circ$ , which represents a combination of the state (enthalpic and entropic) functions ( $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ ), may change only marginally and does not reflect the structural achievements. A remedy to connect the structural modification in a tailored host–guest relationship to the experimental energetics can be expected from isothermal titration calorimetry (ITC). This method allows the pertinent thermodynamic state functions to be obtained along with the stoichiometry of host–guest complex formation from a single experiment.<sup>[5]</sup> Since calorimetric measurements faithfully report on the cumulative heat response of the entire system it is mandatory to design a host–guest system simple enough to allow deconvolution of all the processes happening simultaneously in solution and ascribe the heat effect to just one association reaction. Studying a series of structurally related compounds should unfold the structure–affinity correlation, in addition, and the risk of misinterpretation is lowered by using trend analysis.

The association of bicyclic guanidinium cations (e.g. **1**) with carboxylates **5** (Scheme 1) may provide a suitable host–guest system. The interaction mode follows strict 1:1 stoichiometry



Scheme 1. Overview of the associations between **1–4-X<sup>-</sup>** and **5**.

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and was characterized in solution and in the solid state in numerous examples.<sup>[6]</sup> The prime structural motif which is also frequently found in protein–substrate complexes<sup>[7]</sup> features an almost planar cation–anion arrangement, assisted by two parallel hydrogen bonds as shown by the X-ray crystal structures of the **2**-benzoate and **1**-trifluoroacetate complexes (Figure 1).

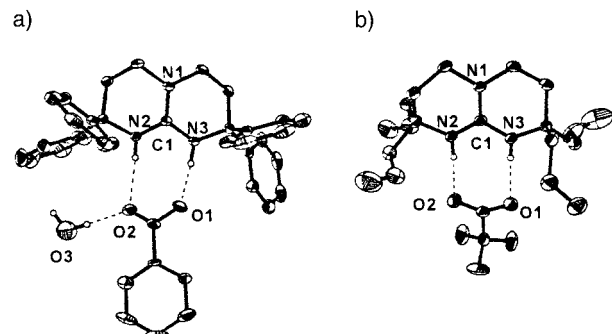


Figure 1. X-ray crystal structure of **2**-benzoate (a) and **1**-trifluoroacetate (b).<sup>[11]</sup> Selected bond lengths [Å] in (a): N2–O2 2.88, N3–O1 2.70, O2–O3 2.77; the orientation of the benzoate was refined using a split model: dihedral angle N1,N2,N3/O1,O2,C2 position 1 with 0.75 occupancy = 29.4°; position 2 with 0.25 occupancy = 59.0°.

Formation of the dedicated hydrogen-bonded ion-pair complex **6** is expected to depend on the competition with solvent. Thus, a non-hydrogen-bonding solvent was chosen that at the same time would minimize unspecific ion pairing by its high dielectric permittivity  $\epsilon$ . Guided by these requirements and the excellent solubility of **5**, dry acetonitrile ( $\epsilon = 36$ ) appeared to be an optimal choice. A typical ITC plot from the titration of **3** with **5** in acetonitrile at 30 °C is depicted in Figure 2. The integration of the heat pulses obtained in each titration step in Figure 2a gives a titration curve (Figure 2b) rendering the molar enthalpy  $\Delta H^\circ$  as the step height and the free energy  $\Delta G^\circ$  from the slope in the inflection point. The stoichiometry  $n$  is derived as an independent parameter from the curve fit, and the molar entropy  $\Delta S^\circ$  may be calculated from the Gibbs–Helmholtz equation.

Competition of the desired guest species with the counter ions is inevitable when using abiotic hosts carrying a charge. Though straightforward deliberations can reduce this interference its influence has occasionally been noted<sup>[8]</sup> but has seldom been quantified. The calorimetric determination of host–guest binding in acetonitrile of the tetraallyl-substituted guanidinium compound **1** with **5** revealed a surprisingly strong dependence on the counter ion (Table 1). Switching the counter anion from chloride to hexafluorophosphate shifts the

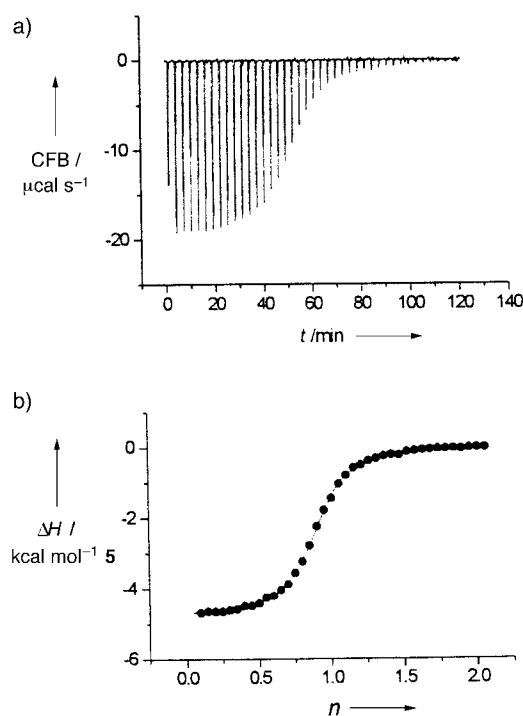


Figure 2. Typical ITC plot of the titration of **3**-PF<sub>6</sub><sup>−</sup> (0.91 mM) with **5** (22.57 mM) in acetonitrile at 30 °C; CFB = cell feedback current.

experimental host–guest affinity by more than a power of ten, with the larger, less hydrogen-bonding anions yielding the higher  $K_{\text{ass}}$  values. The anion influence is easily detectable even at submillimolar concentrations in high dielectric solvent acetonitrile. The clear-cut dependence on charge density points to an unspecific ion-pairing process which is also indicated by inspection of the entropy of host–guest binding. In all cases the association is accompanied by a positive entropy contribution testifying to the inadequacy of the lock-and-key principle<sup>[2]</sup> to explain the experimental outcome. While the combination of just two binding partners to form a tight complex must superficially result in a more negative  $\Delta S^\circ$  because of the loss of degrees of freedom for translation and rotation<sup>[3]</sup> the observation of the opposite result can be explained by the release of solvent molecules and counter ions engaged in the solvation of the binding sites. The contribution of the entropic component  $T\Delta S^\circ$  to the free energy  $\Delta G^\circ$  is not a marginal factor but may even constitute the major part of  $\Delta G^\circ$  (e.g. in the case involving chloride; Table 1). Again a subtle enthalpy–entropy compensation ensures the more drastic change in the association enthalpy  $\Delta H^\circ$  is not expressed in the resulting Gibbs enthalpy  $\Delta G^\circ$ .

Table 1. Thermodynamic state functions, binding affinities  $K_{\text{ass}}$ , and experimental stoichiometries  $n$  of the reactions of **1**<sup>+</sup>–X<sup>−</sup> with **5** in acetonitrile at 30 °C.<sup>[a]</sup>

| X <sup>−</sup>                      | Cl <sup>−</sup>  | Br <sup>−</sup>  | I <sup>−</sup>   | BF <sub>4</sub> <sup>−</sup> | PF <sub>6</sub> <sup>−</sup> |
|-------------------------------------|------------------|------------------|------------------|------------------------------|------------------------------|
| $\Delta H^\circ$ [kcal]             | $-2.93 \pm 0.05$ | $-4.13 \pm 0.02$ | $-4.52 \pm 0.02$ | $-4.58 \pm 0.01$             | $-5.21 \pm 0.01$             |
| $\Delta G^\circ$ [kcal]             | $-6.35 \pm 0.05$ | $-7.03 \pm 0.05$ | $-7.55 \pm 0.05$ | $-7.78 \pm 0.02$             | $-7.73 \pm 0.03$             |
| $\Delta S^\circ$ [e.u.]             | $+11.3 \pm 0.3$  | $+9.5 \pm 0.2$   | $+10.0 \pm 0.2$  | $+10.6 \pm 0.1$              | $+8.3 \pm 0.1$               |
| $T\Delta S^\circ$ [kcal]            | $+3.42$          | $+2.89$          | $+3.03$          | $+3.20$                      | $+2.52$                      |
| $K_{\text{ass}}$ [M <sup>−1</sup> ] | 38000            | 118000           | 280000           | 414000                       | 380000                       |
| $n$                                 | 1.16             | 1.07             | 1.05             | 1.09                         | 1.00                         |

[a] From ITC titrations (the error limits refer to the fit of the data).

The results listed in Table 1 suggest that there is a grading in the formation of ion-pairs between the guanidinium host and the series of counter anions. Chloride forms the most stable complex with the host, thus showing the lowest exothermicity ( $-\Delta H^\circ$ ) in the exchange of chloride for benzoate, while the  $\text{PF}_6^-$  ion, at the other extreme, obviously enables the strongest enthalpic response because of its weak binding to the guanidinium group. There is no direct evidence that the limit of complete dissociation has been reached even with the least hydrogen-bonding ion  $\text{PF}_6^-$  nor that the second process to be considered in the trend analysis, the interaction of the counter anion, released on benzoate binding, with the tetraethylammonium cation, would perturb the result significantly. In fact tetraalkylammonium halides have been characterized as strong electrolytes in acetonitrile<sup>[9]</sup> and any ion pairing there would rather strengthen the differences within the series.

The impact of host design on binding affinity represents the ultimate goal of molecular-recognition studies and this was evaluated using an ensemble of custom-made guanidinium iodides **1–4**.<sup>[10]</sup> All of these compounds contain the same primary binding motif and are probed by complex formation with the same guest species **5**. However, the lining of the binding site was modified synthetically to introduce substituents with different steric properties, but without harming the preferential binding mode. The approach is analogous to the site-directed mutagenesis of biological receptors in which single amino acid residues in the substrate binding pocket may be deliberately exchanged to probe or alter the binding characteristics. Unlike the biological example, in the present artificial host–guest system the substituents available are not restricted to the natural amino acids.

The calorimetric results (Table 2) report a clear trend that assign a *decisive role* to solvation even in a typical organic solvent, such as acetonitrile. We observe a distinct variation of the binding free energy  $\Delta G^\circ$  with the substitution pattern of the host. The differences are manifest in the enthalpies as well as in the entropies of association. The less positive  $\Delta S^\circ$  values seen in **2** and **3** with the aromatic substituents indicate the release of fewer solvent molecules on benzoate binding than in **1** or **4**. In view of the considerable distance of the guest from the residues in the  $\alpha$ -positions of the host (see Figure 1), a direct influence of the guest on the internal motility of the host is unlikely. Thus, it is most plausible to assume that the receptor site in **2** and **3**, lined by aromatic residues, is less solvated than the others and thus the enthalpic penalty paid to disrupt the solvation shell is smaller. This smaller unfavorable contribution results in an enhancement of the total exothermicity. The same arguments serve to explain the energetics of

binding to the hosts **1** and **4**. The tetrasubstitution with “lean” residues directly adjacent to the binding site in **1** or by disubstitution with much more bulky silylether groups in **4** gives states of solvation that seem to be very much alike.

The solvation effects may be supplemented to some degree by a field effect that lowers the dielectric constant in the vicinity of the charged guanidinium function and thereby enhances the coulombic attraction for the anionic guest. For instance, the fluorenyl compound **3** shows solvation changes almost identical to those of the tetraphenyl analogue **2** (cf.  $\Delta S^\circ$  values), but exhibits a significantly enhanced enthalpic contribution. The result relates to the presumed higher rigidity of **3** which opposes the reorientation of the solvent dipoles to cope with the change of the electrostatic field on complex formation.

Comparison of **1** and **2** also provides a good example for the benefit of dissecting  $\Delta G^\circ$  into the enthalpy and entropy components. Considering affinity only ( $K_{\text{ass}}$ ) the allyl compound **1** would be a better host than **2**. Most molecular recognition studies, however, would rather select for better structural definition of the noncovalent complex since this constitutes the basis of goals from selectivity to self-assembly. With respect to precise structuring of the host–guest complex, **2** holds an edge over **1** because of the stronger enthalpic interaction and thus provides a strong argument to take enthalpy instead of the almost exclusively used free energy as a ranking criterion.

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Table 2. Energetics of host–guest binding of the compounds **1–4**·I<sup>−</sup> with benzoate in acetonitrile at 30 °C.<sup>[a]</sup>

|                                     | <b>1</b>         | <b>2</b>         | <b>3</b>         | <b>4</b>         |
|-------------------------------------|------------------|------------------|------------------|------------------|
| $\Delta H^\circ$ [kcal]             | $-4.52 \pm 0.02$ | $-5.18 \pm 0.02$ | $-6.03 \pm 0.03$ | $-4.40 \pm 0.02$ |
| $\Delta G^\circ$ [kcal]             | $-7.55 \pm 0.05$ | $-6.99 \pm 0.04$ | $-8.00 \pm 0.04$ | $-7.35 \pm 0.04$ |
| $\Delta S^\circ$ [e.u.]             | $+10.0 \pm 0.2$  | $+6.0 \pm 0.2$   | $+6.5 \pm 0.2$   | $+9.8 \pm 0.3$   |
| $T\Delta S^\circ$ [kcal]            | $+3.03$          | $+1.81$          | $+1.97$          | $+2.95$          |
| $K_{\text{ass}}$ [M <sup>−1</sup> ] | 280 000          | 111 000          | 592 000          | 203 000          |
| $n$                                 | 1.05             | 1.01             | 1.06             | 0.90             |

[a] From ITC titrations.

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## Characterization of Reactive Intermediates by Diffusion-Ordered NMR Spectroscopy: A Snapshot of the Reaction of <sup>13</sup>CO<sub>2</sub> with [Cp<sub>2</sub>Zr(Cl)H]\*\*

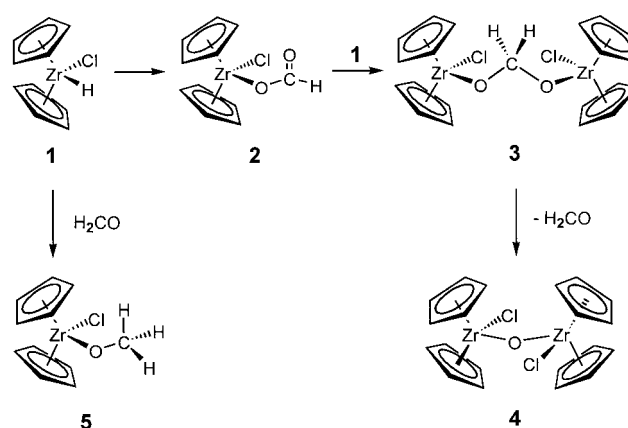
Nils E. Schlörer, Eurico J. Cabrita and Stefan Berger\*

*Dedicated to Professor Anton Rieger on the occasion of his 70th birthday*

In cases in which the structural characterization of reagents generated in situ or of reactive intermediates is not feasible with conventional methods, DOSY (diffusion ordered spectroscopy) NMR spectroscopy provides a valuable method to obtain additional information.<sup>[1]</sup> Until now, pulsed field gradient (PFG) spin-echo NMR experiments were employed mainly in organic and pharmaceutical chemistry for the study of aggregation and binding processes.<sup>[1d, 2]</sup> More recently, however, with the introduction of DOSY NMR spectroscopy the traditional diffusion experiment was subject to a remark-

able advance.<sup>[3]</sup> By presenting the results in a „2D spectrum“—the chemical shift is displayed in one dimension, the diffusion in the other—the resolution and assignment of even complex mixtures are greatly facilitated. The surprising similarity of this concept as well as the manner of presentation led to the description of DOSY NMR spectroscopy as „NMR chromatography“. Although this technique is also extraordinarily well-suited for applications in organometallic and inorganic chemistry in solution, it has attracted little attention.<sup>[4]</sup> Herein we demonstrate the usefulness of DOSY NMR spectroscopy by presenting a new application.

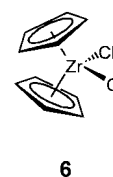
In the course of the present investigation, DOSY NMR spectroscopy has been successfully applied for the first time to determine the molecularity of an intermediate in the reaction of [Cp<sub>2</sub>Zr(Cl)H] (**1**) with CO<sub>2</sub> (Scheme 1). Recently, we



Scheme 1. The investigated reaction of [Cp<sub>2</sub>Zr(Cl)H] (**1**) with CO<sub>2</sub>.

succeeded in elucidating the long-standing postulated mechanism of this reaction by low-temperature NMR spectroscopy studies.<sup>[5, 6]</sup> We were able to observe in situ both the formiato complex **2**, which is formed by insertion of CO<sub>2</sub> into the Zr–H bond of the hydride, and the binuclear diolato complex **3**, which results from reaction with another equivalent of **1**. Although complex **2** was synthesized in an earlier study,<sup>[7]</sup> the existence of the extremely unstable complex **3** was previously only postulated. However, all our attempts to structurally characterize this species by methods other than <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy or to isolate it for a determination of the structure by X-ray structure analysis, failed. Since it was not possible to prove convincingly by spectroscopy that the observed intermediate is a binuclear zirconium compound, we tried to extract additional structural information by means of DOSY NMR spectroscopy.

Prior to studies aimed to characterize intermediate **3**, we examined the suitability of DOSY NMR spectroscopy for such a system by examining the behavior of two model compounds. With the purpose of determining whether the differences between the mono- and binuclear species lead to a resolution in the diffusion dimension in DOSY spectra, we chose a mixture consisting of the binuclear complex **4**, which has a molecular mass that is almost identical to that of the proposed intermediate, and the mononuclear complex **6**. The <sup>13</sup>C



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INEPT DOSY spectrum of this mixture (Figure 1)<sup>[8, 9]</sup> shows a clear resolution of the Cp signals of the two complexes in the diffusion dimension. As expected, the „heavier“, binuclear compound has the smaller self-diffusion coefficient, which allows the definite assignment of the signals to the corresponding complexes.

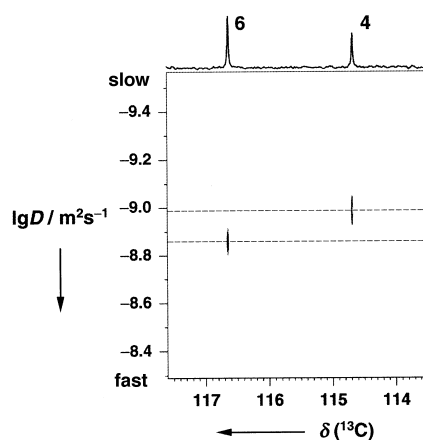


Figure 1. Section of the  $^{13}\text{C}$  INEPT DOSY spectrum of a mixture of **4** and **6** in  $[\text{D}_8]\text{THF}$  (Cp region), measured at  $27^\circ\text{C}$ .

The relationship between diffusion coefficients and structural properties of molecules is based on the dependence of the self-diffusion coefficients on friction factors, which, in turn, depend on molecular size and the viscosity of the solution. If a molecule is considered as a sphere, the diffusion can be described by the Stokes–Einstein equation (1),<sup>[10]</sup> in which  $T$  is the absolute temperature (in K) and  $k_B$  is the

$$D = k_B T / (6\pi\eta r_H) \quad (1)$$

Boltzmann constant, whereas the viscosity of the solvent is given by  $\eta$  and the hydrodynamic radius of a molecule by  $r_H$ . If  $r_H$  and  $\eta$  are known, the self-diffusion coefficient can be estimated from this equation. It is known from earlier studies that self-diffusion coefficients that were calculated by using radii obtained from X-ray data correlate well with experimental values.<sup>[4b]</sup> Therefore, the calculation of self-diffusion coefficients for **4** and **6** was performed by employing radii extracted from X-ray analysis data,<sup>[11]</sup> which yielded values that are in excellent agreement with the experimental results (Table 1).

Following these initial investigations, the reaction of  $^{13}\text{C}$ -labeled  $\text{CO}_2$  with **1** was performed at  $-35^\circ\text{C}$ , as described elsewhere.<sup>[6]</sup> As soon as the signal of **3** reached a sufficient intensity,<sup>[12]</sup> the reaction was stopped by cooling to  $-78^\circ\text{C}$  and  $^{13}\text{C}$  INEPT DOSY NMR spectra were recorded at this temperature (Figure 2).<sup>[9]</sup> The signals assigned to compounds **3** and **5** are depicted. As in the model system investigated before, a clear separation was achieved in the diffusion dimension, allowing for the first time an assignment of the Cp signal of **3**, which was not possible from  $^{13}\text{C}$  NMR spectra.<sup>[13]</sup> Signals of Cp and methoxy carbon atoms in **5** possess the same self-diffusion coefficient, which confirms their origin from the same molecule. As was expected for a binuclear compound,

Table 1. Experimental and calculated diffusion coefficients and hydrodynamic radii of the studied zirconium complexes.

|          | Experimental             |                                   | Calculated         |                                                  |
|----------|--------------------------|-----------------------------------|--------------------|--------------------------------------------------|
|          | $r_H$ [Å] <sup>[c]</sup> | $D$ [ $\text{m}^2\text{s}^{-1}$ ] | $r_H$ [Å]          | $D$ [ $\text{m}^2\text{s}^{-1}$ ] <sup>[c]</sup> |
| <b>6</b> | 3.0                      | $1.61 \times 10^{-9}$             | 3.1 <sup>[a]</sup> | $1.55 \times 10^{-9}$                            |
| <b>4</b> | 3.7                      | $1.31 \times 10^{-9}$             | 3.9 <sup>[a]</sup> | $1.30 \times 10^{-9}$                            |
| <b>5</b> | 4.2                      | $1.55 \times 10^{-10}$            | 3.6 <sup>[b]</sup> | $1.81 \times 10^{-10}$                           |
| <b>3</b> | 6.3                      | $1.05 \times 10^{-10}$            | 6.1 <sup>[b]</sup> | $1.07 \times 10^{-10}$                           |

[a] Calculated from X-ray structure data under the assumption of a spherical shape.<sup>[11]</sup> [b] Calculated from the minimized gas-phase structure (PM3).<sup>[13]</sup> [c] Calculated by using the Stokes–Einstein equation. For the viscosity the values for THF were used at the corresponding temperatures ( $T = 25^\circ\text{C}$  (**6** and **7**),  $T = -78^\circ\text{C}$  (**3** and **5**); the value 2.27 cP, at  $-78^\circ\text{C}$ , was extrapolated from literature data).<sup>[16]</sup>

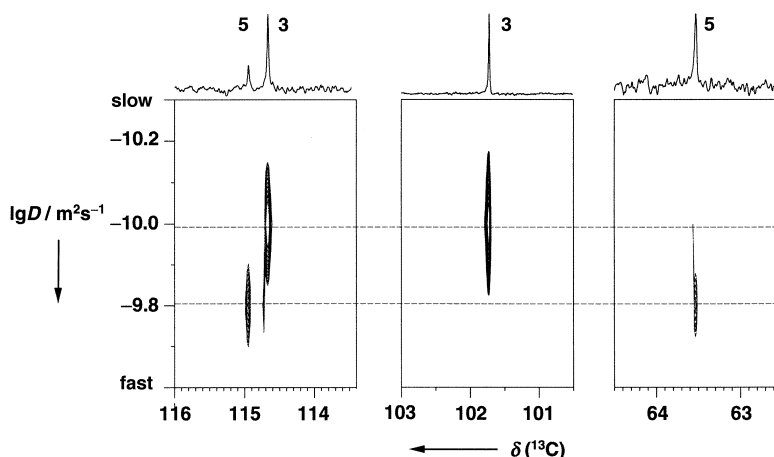


Figure 2.  $^{13}\text{C}$  INEPT DOSY spectrum obtained during the reaction of **1** with  $^{13}\text{C}$ -labeled  $\text{CO}_2$  at  $-78^\circ\text{C}$  in  $[\text{D}_8]\text{THF}$ . The sections show the signals of **3** ( $\delta = 114.6$  (Cp) and  $101.7$  ( $\text{CH}_2$ )) and **5** ( $\delta = 114.9$  (Cp) and  $63.5$  ( $\text{OCH}_3$ )).

the self-diffusion coefficient of intermediate **3**, which was extracted from the signals of Cp and  $\text{CH}_2$  carbon atoms, is smaller. Like in the first case, the experimental data were compared with the estimated self-diffusion coefficients, which were calculated from the Stokes–Einstein equation. For **3** and **5**, no X-ray data were available; therefore, radii from minimized gas-phase structures were used.<sup>[14]</sup> This approach has been previously described for organolithium compounds.<sup>[4a]</sup> Again, the agreement between the experimental and calculated ratio of the self-diffusion coefficients of **3** and **5** is good, especially considering the simplifying models used (Table 1).

With this study it was demonstrated for the first time that DOSY NMR spectroscopy can be applied as a new tool for the characterization of reactive intermediates in organometallic reactions. The straightforward accessibility of this technique, which—if a gradient unit is present—requires no additional equipment, and the simple estimation of self-diffusion coefficients, which is possible without an extended demand on calculations, provide a new tool for the investigation of molecular properties of unstable compounds in solution.

## Experimental Section

NMR experiments were performed on a Bruker DRX 400 spectrometer (9.4 T), equipped with a  $z$  gradient probe head capable of producing



gradients with a strength of 56 G cm<sup>-1</sup>. All spectra were acquired with a 5 mm TBI probehead. For the DOSY experiments the BPPLD<sup>[3, 15]</sup> pulse sequence or a modification of the INEPT–DOSY sequence were used.<sup>[8]</sup> The pulse-field gradients (*g*) were incremented in 32 steps from 2% up to 95% of the maximum gradient strength in a linear ramp. Gradient lengths  $\delta$  between 1.5 and 2.0 ms, diffusion times  $\Delta$  between 90 and 200 ms, and an eddy current delay (*T*<sub>e</sub>) of 5 ms were employed. After Fourier transformation and baseline correction, the diffusion dimension was processed by using the Bruker xwinnmr package (version 3.0) and the diffusion values were read directly from the spectra.

For the experiment with a mixture of **4** and **6**, a solution of **4** (0.013 mmol) and **6** (0.041 mmol) in [D<sub>8</sub>]THF (400  $\mu$ L) was prepared. For the monitoring of the reaction of **1** with <sup>13</sup>CO<sub>2</sub>, **1** (0.050 mmol) and [D<sub>8</sub>]THF (350  $\mu$ L) were placed in a pressure-stable NMR tube (Wilmad 522-PP), degassed, and then frozen. <sup>13</sup>CO<sub>2</sub> (0.060 mmol) was condensed in vacuo on top of the frozen mixture. The tube was sealed and transferred into the precooled magnet.

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## The First Highly Efficient Asymmetric Synthesis of $\alpha$ -Substituted Methyl Sulfonates\*\*

Dieter Enders,\* Nicola Vignola, Otto M. Berner, and Jan W. Bats

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

A number of  $\alpha$ -substituted sulfonic acids with interesting pharmacological properties is known, and numerous compounds of this class have been isolated, synthesized, and tested for their biological activity. For instance, 6-gingesulfonic acid, which shows anti-ulcer activity, was isolated from *Zingiberis Rhizoma*.<sup>[1]</sup> Several  $\alpha$ -substituted sulfonic acids, which are known as semisynthetic  $\beta$ -lactam antibiotics, have been examined with regard to their antibacterial activity.<sup>[2]</sup> Cefsulodin, a representative compound of the semisynthetic cephalosporins, shows potent in vivo antipseudomonal activity against *Pseudomonas aeruginosa*.<sup>[3]</sup> Other compounds such as  $\alpha$ -phosphonosulfonic acid derivatives are known as potent squalene synthase inhibitors.<sup>[4]</sup>

Enantiopure  $\alpha$ -substituted sulfonic acids are also employed in synthesis as strongly acidic resolving agents, especially for free neutral amino acids. For example, (*S*)-(–)-1-phenylethanesulfonic acid ((–)-PES) was found to be an efficient resolving agent for the optical resolution of DL-leucine.<sup>[5]</sup> The related (+)-2-(2,3,4-trichlorophenyl)ethanesulfonic acid ((+)-TCPES) has been used as resolving agent for antifungal sulfoximines.<sup>[6]</sup>

Considering their synthesis, enantiopure  $\alpha$ -substituted sulfonic acids are commonly obtained from the corresponding racemates by resolution techniques with chiral amines.<sup>[7]</sup> To the best of our knowledge, only two stereoselective methods are known for the synthesis of optically active  $\alpha$ -substituted sulfonic acids. Corey et al. reported the conversion of enantiopure (*R*)-1-phenylethanol to ((–)-PES) in a multistep procedure.<sup>[8]</sup> For the synthesis of a squalene synthase inhibitor, the asymmetric  $\alpha$ -alkylation of an  $\alpha$ -phosphonosulfonate bearing the chirality information within the phosphono moiety was employed. To date this is the only known auxiliary-controlled method for the asymmetric synthesis of  $\alpha$ -substituted sulfonates.<sup>[9]</sup>

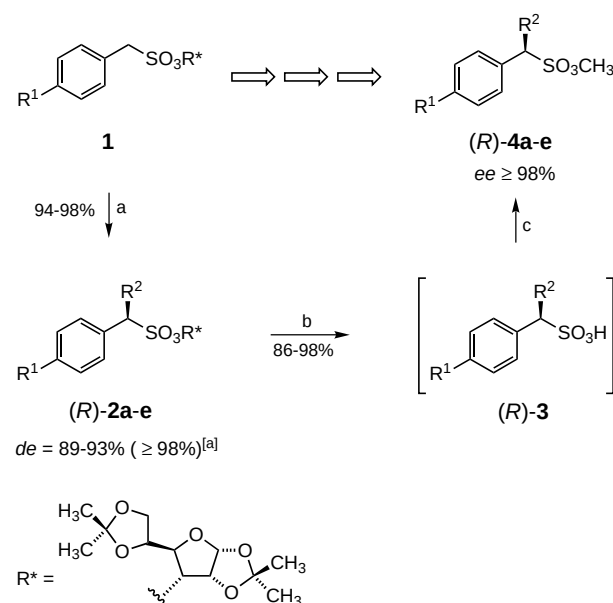
In contrast, no method is known to perform asymmetric  $\alpha$ -alkylations of metalated sulfonic esters prepared from enantiopure alcohols as auxiliaries. A serious problem during metalation of sulfonic esters could be  $\beta$ -elimination under these basic conditions.

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We report here the first asymmetric  $\alpha$ -alkylations of lithiated sulfonic esters bearing a removable enantiopure alcohol auxiliary. As chiral auxiliary 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -D-allofuranose was used, which was synthesized on a 30 g scale from inexpensive 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -D-glucose according to an improved and simple epimerization procedure in 70 % yield.<sup>[10]</sup> This sugar has also been used as a chiral auxiliary in the alkylation of ester enolates,<sup>[11]</sup> but only moderate diastereoselectivities were observed.

We obtained the sulfonates **1** by reaction of the allofuranose derivative with benzylic sulfonyl chlorides, which are commercially available or can be easily prepared from the corresponding sodium sulfonates<sup>[12]</sup> starting from the benzylic bromides.<sup>[13]</sup> As shown in Scheme 1, the enantiopure sulfonates **1** were metalated with one equivalent of *n*-butyllithium



Scheme 1. Asymmetric synthesis of  $\alpha$ -alkylated methyl sulfonates. a) 1. *n*BuLi (1.0 equiv), THF,  $-(90\text{--}95)^\circ\text{C}$ , 1 h; 2.  $\text{R}^2\text{X}$  (1.5 equiv),  $-(90\text{--}95)^\circ\text{C}$ , 1 h,  $-78^\circ\text{C}$ , 24 h; b)  $\text{Pd}(\text{OAc})_2$  (15 mol %), EtOH/ $\text{H}_2\text{O}$ , reflux, 4 d; c)  $\text{CH}_2\text{N}_2$  (ethereal solution). [a] After recrystallization from 2-propanol.

in tetrahydrofuran at  $-(90\text{--}95)^\circ\text{C}$ . At low temperatures any side reactions are minimized, such as the attack of *n*-butyllithium on the sulfonate moiety or a  $\beta$ -elimination of the lithiated alcoholate of the sugar auxiliary. The lithiated sulfonic esters are allowed to react with the electrophiles at  $-(90\text{--}95)^\circ\text{C}$  for one hour and then at  $-78^\circ\text{C}$  for 24 h. Work-up and purification gave the  $\alpha$ -substituted sulfonates **2** in excellent yields (94–98 %) and high diastereomeric excesses of  $de = 89\text{--}93\%$  (Table 1). Virtually diastereomerically pure sulfonates could be obtained by recrystallization from 2-propanol ( $de \geq 98\%$ ).

The configuration of the newly formed stereogenic center was determined to be *R* through single-crystal X-ray structure analysis in the case of product **2d** (Figure 1).<sup>[14]</sup> Since we can postulate a uniform reaction mechanism, all the described examples should possess the same configuration.

Table 1. Asymmetric  $\alpha$ -alkylation of sulfonates **1** to afford sulfonates **2**.

| <b>2</b> | $\text{R}^1$ | $\text{R}^2$      | Yield [%] | $de[\%]^{\text{[a,b]}}$ | $[\alpha]_{\text{D}}^{\text{[c]}}$ |
|----------|--------------|-------------------|-----------|-------------------------|------------------------------------|
| <b>a</b> | H            | methyl            | 95        | 91 ( $\geq 98$ )        | + 91.3                             |
| <b>b</b> | H            | allyl             | 93        | 90 ( $\geq 98$ )        | + 77.0                             |
| <b>c</b> | H            | benzyl            | 94        | 89 ( $\geq 98$ )        | + 34.4                             |
| <b>d</b> | <i>t</i> Bu  | benzyl            | 95        | 91 ( $\geq 98$ )        | + 22.6                             |
| <b>e</b> | <i>t</i> Bu  | (2-naphtyl)methyl | 98        | 93 ( $\geq 98$ )        | + 3.8                              |

[a] Values in parentheses after recrystallization from 2-propanol. [b] Determined by  $^{13}\text{C}$  NMR spectroscopy. [c] All optical rotations were measured in Uvasol grade  $\text{CHCl}_3$  with concentrations of 1.0 at room temperature.

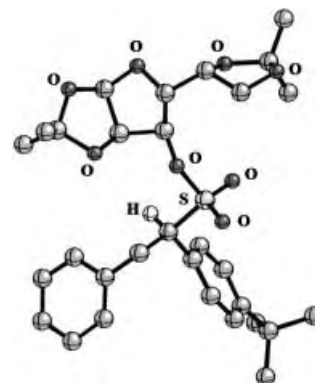


Figure 1. X-ray crystal structure of **2d**.<sup>[14]</sup>

Finally, many procedures were screened for an efficient racemization-free cleavage of the auxiliary. The best results were achieved by refluxing the sulfonates **2** in an EtOH/ $\text{H}_2\text{O}$  solution containing 15 mol %  $\text{Pd}(\text{OAc})_2$  for four days.<sup>[15]</sup> To isolate the final products in a more accessible form, the sulfonic acids **3** were directly converted with diazomethane to the corresponding title methyl sulfonates (*R*)-**4**,<sup>[16]</sup> which were obtained in very good yields and as pure stereoisomers (Scheme 1, Table 2).

To explain the high diastereofacial selectivity of the electrophilic substitutions in the  $\alpha$ -position to the sulfonate function, the solution structure and aggregation of the lithiated chiral sulfonates remains to be determined.

In conclusion, the novel protocol provides an efficient and first practical route to optically active  $\alpha$ -substituted methyl sulfonates. The asymmetric  $\alpha$ -alkylation and the removal of the auxiliary proceed in good overall yields and lead to the final products in excellent enantiomeric excesses. The highly enantioenriched title compounds are valuable substrates for

Table 2. Removal of the chiral auxiliary to form the title methyl sulfonates **4**.

| ( <i>R</i> )- <b>4</b> | $\text{R}^1$ | $\text{R}^2$      | Yield [%] | $ee[\%]^{\text{[a]}}$ | $[\alpha]_{\text{D}}^{\text{[b]}}$ |
|------------------------|--------------|-------------------|-----------|-----------------------|------------------------------------|
| <b>a</b>               | H            | methyl            | 98        | $\geq 98$             | + 25.6                             |
| <b>b</b>               | H            | allyl             | 90        | $\geq 98$             | – 6.3                              |
| <b>c</b>               | H            | benzyl            | 94        | $\geq 98$             | – 77.4                             |
| <b>d</b>               | <i>t</i> Bu  | benzyl            | 88        | $\geq 98$             | – 92.8                             |
| <b>e</b>               | <i>t</i> Bu  | (2-naphtyl)methyl | 86        | $\geq 98$             | – 108.2                            |

[a] Determined by HPLC using a chiral stationary phase ((*R*)-**4a**: Daicel OJ, *n*-heptane/2-propanol 85/15; (*R*)-**4b**: Whelk O1, *n*-heptane/2-propanol 95/5; (*R*)-**4c–e**: Daicel OD 2, *n*-heptane/2-propanol 95/5). [b] All optical rotations were measured in Uvasol grade  $\text{CHCl}_3$  with concentrations of 1.0 at room temperature.

further synthetic transformations, which are currently being investigated in our laboratory.

### Experimental Section

Typical procedure for the  $\alpha$ -alkylation: The enantiopure sulfonate **1** (1 mmol) was dissolved in dry THF (20 mL) and the solution cooled to  $-(90-95)^{\circ}\text{C}$ . After 30 min  $n\text{BuLi}$  (1.0 equiv) was added dropwise. The solution was stirred for an additional hour after which the electrophile (1.5 equiv in 5 mL THF) was added dropwise. The mixture was stirred for 1 h at  $-(90-95)^{\circ}\text{C}$ , then at  $-78^{\circ}\text{C}$ . After 24 h the reaction was quenched by adding pH 7 buffer (2 mL). The mixture was partitioned between  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$  and washed with brine. The aqueous layer was then extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ( $\text{SiO}_2$ , pentane/diethyl ether).

Typical procedure for the removal of the chiral auxiliary: The sulfonate **2** (0.6 mmol) was dissolved in an  $\text{EtOH}/\text{H}_2\text{O}$  solution (19 mL/1 mL).  $\text{Pd}(\text{OAc})_2$  (15 mol %) was added to the solution and the mixture was refluxed for four days (TLC control). The palladium residues were removed by filtration and washed twice with  $\text{EtOH}$ . The filtrate was treated with an ethereal solution of diazomethane until the yellow color persisted. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography ( $\text{SiO}_2$ , pentane/diethyl ether).

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### Protonated Sulfuric Acid: Preparation of Trihydroxyoxosulfonium Hexafluoroantimonate $\text{H}_3\text{SO}_4^+ \text{SbF}_6^-$

Rolf Minkwitz,\* Raphael Seelbinder, and René Schöbel

Dedicated to Professor Karl Otto Christe on the occasion of his 65th birthday

One of the strongest acids is 100% sulfuric acid and this marks per definition the border to the superacids. Among the ions that are formed by the autoprotolysis of sulfuric acid according to Equation (1), only the structure of the hydrogensulfate ion in solid salts and that of sulfuric acid itself is known.<sup>[1, 2]</sup>



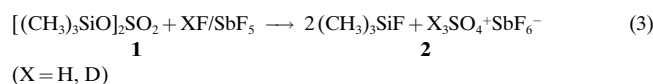
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The existence of the trihydroxyoxosulfonium cation  $\text{H}_3\text{SO}_4^+$  was confirmed by cryoscopy, conductivity measurements, and mass spectrometry, and structural parameters were calculated by theoretical methods.<sup>[3–5]</sup> A complete protonation of sulfuric acid to  $\text{H}_3\text{SO}_4^+$  is only possible by acids with a proton activity  $H_0$  about six orders of magnitude greater than that of  $\text{H}_2\text{SO}_4$ . Theoretically the superacid  $\text{HF/SbF}_5$  with a  $H_0$  value of up to  $-21$  should be able to protonate sulfuric acid, which has a  $H_0$  value of  $-12$ , to give the  $\text{H}_3\text{SO}_4^+$  ion. But it was shown by Gillespie and Robinson that about 0.1 % of the sulfuric acid also undergoes an ionic self-dehydration [Eq. (2)] at the same time to give oxonium ions.<sup>[5]</sup>



Oxonium ions have a levelling effect on the superacid strength, which prohibits a complete protonation, as we confirmed by our own investigations. The reaction of pure sulfuric acid with  $\text{HF/SbF}_5$  does not yield a homogeneous solid but a highly viscous residue, from which  $\text{H}_3\text{O}^+\text{SbF}_6^-$  can be isolated. To avoid the dehydration leading to formation of  $\text{H}_3\text{O}^+$  ions, the bis(trimethylsilyl) ester of sulfuric acid (**1**) was used as starting material, which reacts according to Equation (3).



This kind of reaction was successfully applied to the preparation of salts of protonated hydrogen peroxide and protonated carbonic acid.<sup>[6, 7]</sup> The formation of **2** is thermodynamically favored because of the high formation enthalpy of the Si–F bond and its preparation has the advantage that trimethylfluorosilane and HF can be removed easily at  $-78^\circ\text{C}$  in vacuum.  $^1\text{H}$  NMR spectroscopy gave no indication of the formation of  $\text{H}_3\text{O}^+$  ions and thus for a reaction according to Equation (2); the spectrum shows only a singlet at  $\delta = 12.1$  for  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$ . After removal of **2** and excess of HF/DF a crystalline, colorless solid of  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  or  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$ , respectively, precipitates, from which crystals suitable for an X-ray structure analysis were obtained.<sup>[8]</sup> In contrast to  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$ , the results of the X-ray structure analysis of  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  did not lead to a satisfactory determination of the structure because all measured crystals displayed a disorder that we were unable to explain.

Efforts to obtain the compounds as hexafluoroarsenate salts by the use of the superacid  $\text{XF/AsF}_5$  (X = H, D) were not successful and always yielded a highly viscous fluid, in which no oxonium salts were found. Evidently, the acid strength of this system is not sufficient to protonate the sulfuric acid completely.

The single-crystal structure determination of  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  shows, within the precision of the measurement, that three of the four S–O bonds are almost the same length (149.9(6)–151.2(6) pm). They are shorter than the S–O single bonds in sulfuric acid (153.7(1) pm) and longer than its S–O double bond, which infers delocalization of the positive charge over the  $\text{SO}_3$  unit (Figure 1, Table 1). The length of the S–O double

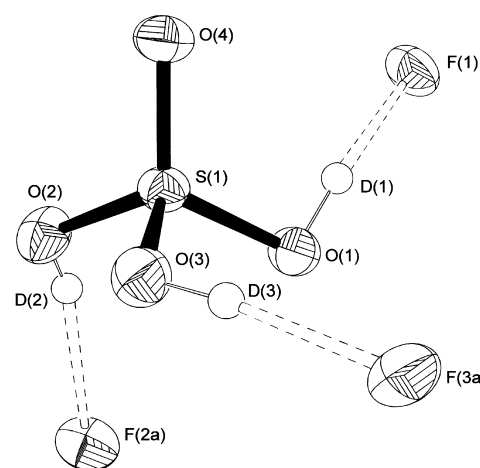


Figure 1. The  $\text{D}_3\text{SO}_4^+$  ion with atom labels. Interionic contacts [pm]: O(1)–D(1)···F(1) 259.3(8), O(2)–D(2)···F(2a) 254.5(8), O(3)–D(3)···F(3a) 255.7(8). Symmetry operation: a:  $-x, -y, -z$ .

Table 1. Selected bond lengths and angles of  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$ . Only three F atoms are shown from the anion in Figure 1.<sup>[a]</sup>

| Distances [pm] |          | Angles [°]      |          |
|----------------|----------|-----------------|----------|
| S(1)–O(1)      | 151.1(5) | O(4)–S(1)–O(1)  | 115.6(3) |
| S(1)–O(2)      | 149.8(6) | O(4)–S(1)–O(2)  | 110.5(4) |
| S(1)–O(3)      | 150.6(6) | O(4)–S(1)–O(3)  | 115.7(3) |
| S(1)–O(4)      | 141.0(6) | O(1)–S(1)–O(2)  | 107.3(3) |
|                |          | O(1)–S(1)–O(3)  | 103.6(3) |
|                |          | O(2)–S(1)–O(3)  | 103.0(3) |
| Sb(1)–F(1)     | 188.9(5) | F(1)–Sb(1)–F(5) | 177.3(2) |
| Sb(1)–F(2)     | 191.4(5) | F(2)–Sb(1)–F(6) | 179.2(2) |
| Sb(1)–F(3)     | 190.4(5) | F(2)–Sb(1)–F(3) | 88.0(2)  |
| Sb(1)–F(4)     | 187.1(5) | F(3)–Sb(1)–F(4) | 176.0(2) |
| Sb(1)–F(5)     | 185.8(5) |                 |          |
| Sb(1)–F(6)     | 186.9(5) |                 |          |

[a] Standard deviations refer to the last digit of the number.

bond in  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  (141.3(6) pm) is comparable to the bond length in solid sulfuric acid (142.6(1) pm).<sup>[2]</sup> All deuterium atoms were found by Fourier synthesis. The Sb–F distances (Sb(1)–F(1) 188.9(5), Sb(1)–F(2) 191.4(5), Sb(1)–F(3) 190.4(5) pm) of the fluorine atoms that participate in the hydrogen (deuterium) bonds are significantly longer than the other Sb–F bond lengths (185.8(5)–187.1(5) pm), thus the anion is a distorted octahedron. Anions and cations are linked by three hydrogen bonds in the crystal, leading to 4-rings comprising 16 atoms. These rings are condensed to wavy bands arranged parallel to the *bc* plane (Figure 2).

The vibrational spectroscopic characterization of  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  and  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  is given by their IR spectra, because during Raman investigations strong fluorescence occurred. The IR spectra (Figure 3, Table 2) of  $\text{X}_3\text{SO}_4^+\text{SbF}_6^-$  (X = H, D) confirm the results of the X-ray structure analysis and are comparable to the spectra of the isoelectronic orthophosphoric acid. The position and contour of the bands, as well as their splitting is attributed to crystal effects. The broad band between 2173 and 2411  $\text{cm}^{-1}$  is assigned to the O–D stretching modes ( $\text{D}_3\text{PO}_4$ : 2050–2350  $\text{cm}^{-1}$ ).<sup>[9]</sup> The

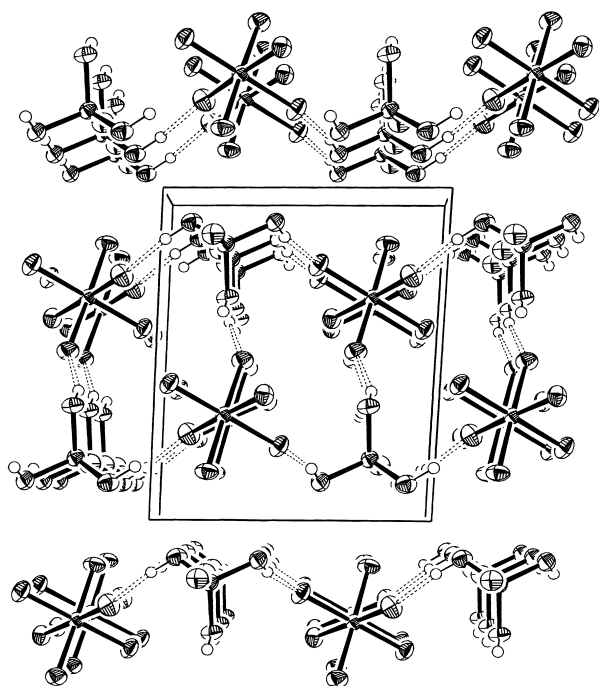


Figure 2. Section of the crystal packing of  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$ .

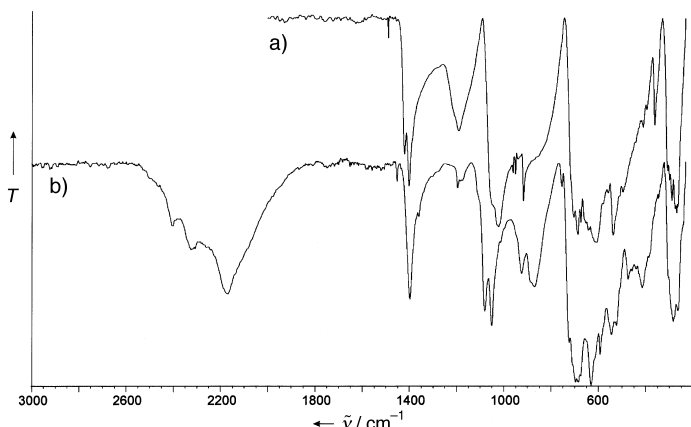


Figure 3. IR spectra of a)  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  and b)  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  as solids at  $-40^\circ\text{C}$ .

S–O stretching mode ( $1401\text{ cm}^{-1}$ ) of the double bond occurs about 340 wavenumbers above the P–O valence mode of phosphoric acid ( $1165\text{ cm}^{-1}$ ), but lower than in the isoelectronic trifluorooxosulfonium cation in the hexafluoroantimonate salt ( $1540\text{ cm}^{-1}$ ).<sup>[10]</sup> The asymmetric  $\text{SO}_3$  valence stretches are detected at  $1051$  and  $1085\text{ cm}^{-1}$  for  $\text{D}_3\text{SO}_4^+$  and at  $1123\text{ cm}^{-1}$  for the protonated sulfuric acid, whereas the symmetric valence modes are found at  $930$  and  $922\text{ cm}^{-1}$ , respectively ( $\text{D}_3\text{PO}_4$ :  $\nu_{\text{as}}(\text{PO}_3)$ :  $1012$ ,  $\nu_{\text{s}}(\text{PO}_3)$ :  $880\text{ cm}^{-1}$ ;  $\text{H}_3\text{PO}_4$ :  $\nu_{\text{as}}(\text{PO}_3)$ :  $1066$ – $1074$ ,  $1007$ ,  $\nu_{\text{s}}(\text{PO}_3)$ :  $885\text{ cm}^{-1}$ ). The  $\text{SO}_3$  deformation modes for  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  are detected at  $482\text{ cm}^{-1}$  for  $\delta_{\text{as}}$  and at  $417\text{ cm}^{-1}$  for  $\delta_{\text{s}}$ . For  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$  only one deformation mode at  $410\text{ cm}^{-1}$  was observed.

Table 2. IR frequencies<sup>[a]</sup> [ $\text{cm}^{-1}$ ] and assignment.

| $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$ | $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$ | Assignment                       |
|-----------------------------------------|-----------------------------------------|----------------------------------|
| n.o.                                    | 2411 (w)                                | } $\nu\text{ OH(D)}$             |
|                                         | 2328 (m)                                |                                  |
|                                         | 2173 (s)                                |                                  |
| 1401 (s)                                | 1401 (s)                                | $\nu\text{ S=O}$                 |
| 1195 (m)                                |                                         | $\delta_{\text{as}}\text{ SOH}$  |
| 1123 (vs)                               |                                         |                                  |
|                                         | 1085 (s)                                | } $\nu_{\text{as}}\text{ SO}_3$  |
|                                         | 1051 (s)                                |                                  |
| 954 (s)                                 |                                         | $\delta_{\text{s}}\text{ SOH}$   |
| 922 (s)                                 | 930 (m)                                 | $\nu_{\text{s}}\text{ SO}_3$     |
|                                         | 872 (s)                                 | $\delta_{\text{as}}\text{ SOD}$  |
|                                         | 546 (s)                                 | } $\delta\text{ O=SO}$           |
| 539 (vs)                                | 521 (sh)                                |                                  |
|                                         | 482 (m)                                 | $\delta_{\text{as}}\text{ SO}_3$ |
| 410 (m)                                 | 417 (m)                                 | $\delta_{\text{s}}\text{ SO}_3$  |
| 361 (m)                                 |                                         | $\delta_{\text{as}}\text{ OSOH}$ |
|                                         |                                         | $\delta_{\text{as}}\text{ OSOD}$ |
| 688 (vs)                                | 280 (s)                                 | } $\nu\text{ SbF}_6^-$           |
| 610 (vs)                                | 684 (vs)                                |                                  |
| 559 (sh)                                | 630 (vs)                                |                                  |
| 287 (s)                                 | 588 (s)                                 |                                  |
|                                         | 287 (s)                                 |                                  |
|                                         |                                         |                                  |

[a] n.o. not observed; intensities (in parentheses): vs = very strong, s = strong, m = medium, w = weak, sh = shoulder.

One expects two vibrations for the  $\text{SbF}_6^-$  ion, but in both salts four vibrations are found. This is attributed to the decrease of the symmetry of the octahedron, which results from the different Sb–F bond lengths as established already in the crystal structure analysis.

#### Experimental Section

$(\text{Me}_3\text{SiO})_2\text{SO}_2$  was prepared according to reference [11].  $\text{SbF}_5$  (Fluka) was triply distilled; DF was prepared from  $\text{D}_2\text{SO}_4$  and  $\text{CaF}_2$  and dried over  $\text{F}_2$ .

In a KEL-F reactor  $\text{SbF}_5$  (1.5 mmol) was dissolved in HF or DF (ca. 140 mmol) and cooled to  $-196^\circ\text{C}$ . Under a dry nitrogen atmosphere  $(\text{Me}_3\text{SiO})_2\text{SO}_2$  (1.5 mmol) was added. The mixture was allowed to warm to  $-78^\circ\text{C}$  and volatile products as well as the excess of HF/DF were removed in dynamic vacuum.  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  or  $\text{H}_3\text{SO}_4^+\text{SbF}_6^-$ , respectively, precipitated as colorless solids, which decomposed at  $-5^\circ\text{C}$ .

Apparatus employed: Raman: Jobin-Yvon T64000, Ar<sup>+</sup>-Laser ( $\lambda = 514.5\text{ nm}$ ) Spectra Physics; IR: Bruker-IFS 113v; NMR: Bruker DPX300; X-ray diffractometer: Nonius-Kappa-CCD ( $1152 \times 1242$  Pixel).

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crystal X-ray analysis of  $\text{D}_3\text{SO}_4^+\text{SbF}_6^-$  at 173 K: triclinic, space group  $P\bar{1}$  (no. 2),  $a = 505.9(1)$ ,  $b = 790.7(1)$ ,  $c = 963.9(1)$  pm,  $\alpha = 86.88(1)$ ,  $\beta = 74.98(1)$ ,  $\gamma = 88.89(1)^\circ$ ,  $Z = 2$ ,  $V = 371.8(1) \times 10^6 \text{ pm}^3$ ,  $\rho_{\text{calc}} = 2.991(1) \text{ g cm}^{-3}$ , crystal dimensions:  $0.15 \times 0.12 \times 0.12 \text{ mm}^3$ ,  $2\theta/\omega$  scans,  $2\theta_{\text{max}} = 54.92^\circ$ ,  $T = 173(2) \text{ K}$ , reflections collected 2543, 1639 independent reflections,  $\sigma$ -limit 2.0,  $\mu(\text{Mo}_{\text{K}\alpha}) = 5.433 \text{ mm}^{-1}$ , structure solution: Patterson method, difference Fourier synthesis; SHELXS-86, SHELXL-93, PARST, PLATON, MISSYM, DENZO, SCALEPACK; 112 free parameters, deuterium atoms from the difference Fourier map  $\Delta F$ ,  $R = 0.0476$ ,  $wR2 = 0.1601$ ,  $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ , structure refinement: full-matrix least-squares on  $F^2$ , largest difference peak and hole  $-2.61/1.36 \text{ e \AA}^{-3}$  from difference Fourier synthesis. For technical reasons we are not able to perform an

experimental absorption correction. Using the data reduction software SCALEPACK (Minor and Otwinowski), each measured frame is multiplied by a certain scale factor that is generated by comparing the intensity of symmetrically related reflections.<sup>[12]</sup> Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-412007.

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# Direct Observation of a Cytosine Analogue that Forms Five Hydrogen Bonds to Guanosine: Guanidino G-Clamp\*\*

Christopher J. Wilds, Martin A. Maier, Valentina Tereshko, Muthiah Manoharan,\* and Martin Egli\*

The two main factors that stabilize pairing between nucleic acid strands are stacking interactions and hydrogen bonding,<sup>[1]</sup> properties that form the basis for biomolecular recognition. Our understanding of recognition has spurred the development of antisense molecules (molecules complementary to a coding oligonucleotide sequence) as potential therapeutics.<sup>[2]</sup> Although modified oligonucleotides offer unparalleled potential in terms of binding selectivity, there are still numerous obstacles to overcome in terms of nuclease resistance, optimum induction of RNaseH activity, uptake into cells, and tissue distribution. While the phosphodiester linkage and sugar moiety have been modified extensively, modifications to the heterocyclic base have been relatively limited as it is necessary to maintain the specific hydrogen-bonding motifs required for base-pair specificity.<sup>[3]</sup>

Some heterocyclic modifications have been shown to enhance the binding affinity of nucleic acids through increased hydrogen bonding and/or base-stacking interactions. Examples include 2,6-diaminopurine, that allows for a third hydrogen bond with thymidine, and replacement of the hydrogen atom at the C5 position of pyrimidine bases with a propynyl group that allows increased stacking interactions.<sup>[4, 5]</sup> Matteucci and co-workers recently reported the synthesis and binding properties of a cytosine analogue termed G-clamp (Figure 1A).<sup>[6, 7]</sup> For a decamer DNA sequence, a single incorporation of a G-clamp was found to increase the melting temperature  $T_m$  of the DNA duplex by 18 °C. Antisense inhibition by RNaseH cleavage has been observed for a phosphorothioate oligonucleotide containing a single G-clamp, which illustrates its potential for sequence-specific

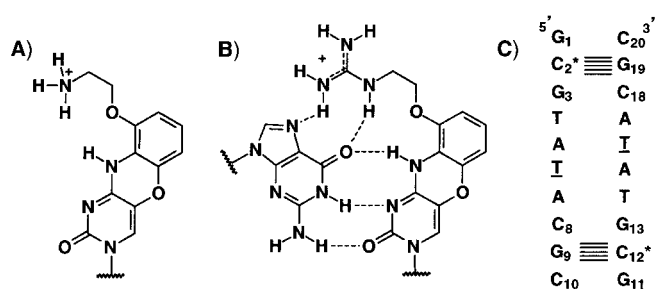


Figure 1. Structure of the tricyclic cytosine analogue G-clamp<sup>[5]</sup> (A), of its extended analogue guanidino G-clamp hybridized to complementary guanosine (B), and of the palindromic decamer duplex crystallized for this study (C). The five hydrogen bonds formed between C\* and G are indicated by horizontal lines (C\* = guanidino G-clamp, T = 2'-O-MOE-T).

downregulation of mRNA.<sup>[6, 7]</sup> This modification is assumed to stabilize the duplex through the formation of an additional hydrogen bond to O6 from the Hoogsteen side. It may also enhance stacking as a result of a larger surface area. Unfortunately, no high-resolution structure is available to date to confirm the existence of the presumed binding motif.

The guanidino G-clamp modification 9-(2-guanidinoethoxy)-phenoxazine was designed to allow for additional hydrogen bonds to the O6 and N7 Hoogsteen binding sites of guanosine (Figure 1B). Binding studies of DNA oligomers containing a single guanidino G-clamp unit to an RNA target revealed an increase in  $T_m$  of 16 °C relative to the unmodified DNA, slightly lower than the  $\Delta T_m$  observed for the original G-clamp modification (see Supporting Information). To investigate the structural properties of this modification we determined the X-ray crystal structure of a modified decamer duplex with the sequence GC\*GTAT<sub>MOE</sub>ACGC, where C\* is the guanidino G-clamp and T<sub>MOE</sub> is a 2'-O-methoxyethyl thymine (Figure 1C).<sup>[8–10]</sup> Crystals of this decamer duplex were grown by the hanging-drop vapor-diffusion method. Data collection was performed at a synchrotron source and data collection and refinement statistics are listed in Table 1.

The overall structure of this duplex is A-form as a result of 2'-O-methoxyethyl thymine units at positions 6 and 16 in the duplex. An A-form environment is desirable to study the structure of nucleic acid modifications for antisense purposes. As illustrated in the case of base pair C12\*–G9 (Figure 2), electron density around the heterocycles clearly shows the two Hoogsteen-type hydrogen bonds formed between the amino and imino nitrogen atoms of the tethered guanidinium

Table 1. Reflection data and refinement statistics.

| Resolution [Å] | N (unique) | Mean [I/σ(I)] | [%] Complete | R-factor <sup>[a]</sup> |
|----------------|------------|---------------|--------------|-------------------------|
| 10.00–3.00     | 1073       | 26.90         | 98.8         | 0.168                   |
| 3.00–2.50      | 768        | 31.51         | 99.9         | 0.142                   |
| 2.50–2.00      | 1722       | 34.38         | 100.0        | 0.133                   |
| 2.00–1.80      | 1288       | 36.70         | 100.0        | 0.116                   |
| 1.80–1.60      | 2005       | 30.33         | 99.9         | 0.102                   |
| 1.60–1.40      | 3314       | 27.90         | 100.0        | 0.115                   |
| 1.40–1.20      | 5804       | 24.68         | 100.0        | 0.115                   |
| 1.20–1.10      | 4680       | 20.08         | 100.0        | 0.116                   |
| 1.10–1.00      | 6666       | 14.35         | 99.6         | 0.130                   |
| All data       | 27 320     | 23.63         | 99.6         | 0.128                   |

[a] R-factor =  $\sum |F(hkl)_o - F(hkl)_c| / \sum F(hkl)_o$ ; no  $\sigma$  cutoff was used.

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

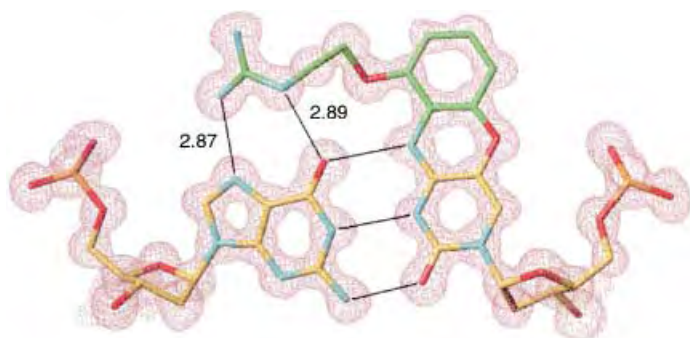


Figure 2. Fourier ( $2F_o - F_c$ ) sum electron-density map (contoured at  $1.25\sigma$ ) around C12\* and G9 confirming formation of five hydrogen bonds (indicated by thin solid lines, selected distances shown [Å]). Red: oxygen, blue: nitrogen, orange: phosphorus, yellow: carbon, green: carbons of the modification.

and O6 and N7 of guanosine, respectively. The hydrogen bond lengths are 2.89 and 2.87 Å and the lengths of the corresponding hydrogen bonds in base pair C2\*–G19 are 2.88 Å and 2.92 Å, respectively. The quality of the electron density data around individual atoms of the phenoxazine ring and tethered group demonstrates that this modification is well ordered and does not assume random conformations. There is some buckling of modified base pairs relative to the other base pairs in the duplex (not shown). This out-of-plane distortion of the base pair between the guanidino G-clamp and G may be a consequence of the requirement to optimize the geometry of both the Watson–Crick and Hoogsteen-type hydrogen bonds within the geometric boundaries provided by the guanidinium ethoxy moiety. In addition, the observed arrangements help to avoid a steric contact between O6 of G and the ethoxy-linker oxygen of the G-clamp (Figure 1 and 2).

The presence of the tricyclic G-clamp moiety results in a considerable improvement of intra-strand stacking at the GpC\* step compared with stacking between cytosine and the 5'-adjacent base (G1 and G11, respectively). The overlap between G1 and C2\* is depicted in Figure 3. While the "cytosine core" displays relatively little stacking to the guanosine base, the remainder of the phenoxazine ring system virtually covers the entire guanosine base. However, while stacking between G-clamp and the base to the 5'-side is improved, stacking to the 3'-adjacent base is not affected by incorporation of the modified base.

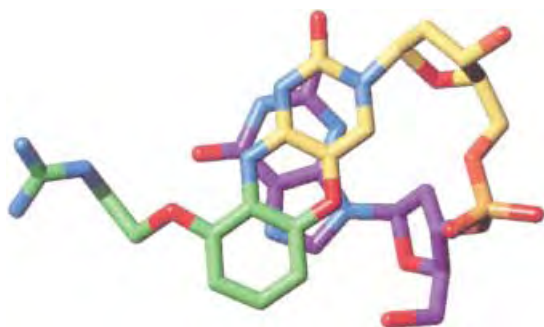


Figure 3. Stacking between G1 and C2\*, viewed approximately along the vertical to the phenoxazine rings. Carbon atoms of G1 are shown in magenta, carbon atoms of the cytosine core of C2\* are shown in yellow and the remainder of the carbon atoms are in green.

Placement of the positively charged guanidinium moiety in the center of the major groove, a site of strong negative potential, results in a significant electrostatic contribution to stability. Moreover, the guanidinium group and phosphates from opposite strands are relatively closely spaced. The average distance between the imino nitrogens of C\* and O2P oxygens of phosphate units is 5.8 Å. Although too long for direct salt bridges, water molecules link guanidinium and phosphate groups. For C12\*, single water molecules mediate contacts between guanidinium imino nitrogens and O2P oxygens of residues C8 and G9.

Interactions between positively charged amines and the Hoogsteen binding site of guanosine are well known. For example, X-ray crystallographic studies of the  $\lambda$  repressor bound to duplex DNA revealed specific contacts between a lysine and the O6 position of G.<sup>[11, 12]</sup> The interactions in the structure of the guanidino G-clamp here are similar to the bidentate hydrogen bonding of the arginine fork with the N7 and O6 positions of guanine observed in zinc fingers from Zif268 (a mouse immediate early protein).<sup>[13]</sup>

Two crucial stabilizing factors of this modification are an increase in the number of hydrogen bonds and improved stacking interactions. Additional contributions to stability are favorable electrostatic interactions and well-ordered water networks. It is difficult to discern if one of these contributions plays a more important role than the others. Binding studies of oligomers with the phenoxazine moiety alone showed moderate increases in  $T_m$  of 2–7 °C.<sup>[14]</sup> Stability was increased most when several phenoxazine groups were clustered together on the same strand, allowing for tricyclic–tricyclic stacking interactions. In the case of an acyclic G-clamp modification, no enhancement in binding was observed. Only when both the phenoxazine and tethered amino group were present was a drastic improvement in binding observed.<sup>[6]</sup> Clearly, hydrogen bonds from the guanidinium group maintain the guanidino G-clamp modification in a position that allows stacking interactions and formation of stable water networks. In the absence of an analogous crystal structure of the duplex containing the original G-clamp modification, it is difficult to hypothesize what the origin of the slight destabilization of the guanidino G-clamp relative to the original amino G-clamp might be.

To summarize, this is the first report of a single base pair within a nucleic acid duplex combining Watson–Crick and Hoogsteen binding to a total number of five hydrogen bonds. Further evaluation of the antisense therapeutic and diagnostic applications of this novel guanidino G-clamp modification is in progress.

## Experimental Section

**Crystallization** by the hanging-drop vapor-diffusion method using commercially available screens (Hampton Research, Laguna Niguel, CA): A 2  $\mu$ L droplet (1.2 mM DNA, 5 % 2-methyl-2,4-pentanediol (MPD), 20 mM Na cacodylate pH 6.0, 6 mM spermine · 4HCl, 40 mM NaCl, 6 mM KCl, 10 mM MgCl<sub>2</sub>) was equilibrated against a reservoir of 1 mL 35 % v/v MPD. Crystals suitable for X-ray diffraction grew in one week.

**Data Collection and Processing:** A crystal (0.7 × 0.2 × 0.2 mm) was picked up from a droplet with a nylon loop and transferred into a cold N<sub>2</sub> stream (120 K). High- and low- resolution data sets were collected on the 5-ID



beam line ( $\lambda = 0.978 \text{ \AA}$ ) of the DND-CAT at the Advanced Photon Source, Argonne, IL, using a MARCCD detector. Data were integrated and merged with DENZO/SCALEPACK.<sup>[15]</sup> Space group  $P2_12_12_1$ ; cell dimensions  $a = 24.52$ ,  $b = 43.02$ ,  $c = 46.68 \text{ \AA}$ . The overall  $R_{\text{merge}}$  for all reflections between 20 and  $1 \text{ \AA}$  was 4.7%.

Structure Determination and Refinement: The structure was solved by molecular replacement using the DNA decamer described in ref. [16] as the initial model and refined with the programs CNS<sup>[17]</sup> and SHELX-97.<sup>[18]</sup> After monitoring the  $R_{\text{free}}$  using 10% of the reflections, all reflections were included in the final rounds of isotropic refinement. Hydrogen atoms were added in SHELX-97 and all atoms including the spermine molecule and solvent water molecules were treated anisotropically. Coordinates and structure factors have been deposited in the Protein Data Bank (accession code 1KGG).

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## De Novo Protein Surface Design: Use of Cation– $\pi$ Interactions to Enhance Binding between an $\alpha$ -Helical Peptide and a Cationic Molecule in 50% Aqueous Solution\*\*

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Ernest Giralt, and Andrew D. Hamilton\*

We have previously shown that synthetic guanidinium-based receptors (such as **1**; Scheme 1) can recognize aspartate- and glutamate-containing peptides in 10% aqueous methanol.<sup>[1–5]</sup> The principal driving force for binding was ion pairing and hydrogen bonding between the carboxylate and guanidinium groups that leads, with optimal matching of the sequence, to peptide stabilization in a helical conformation. In order to extend this approach to targets of more biological relevance we sought to identify peptide sequences that could recognize the receptor with increased affinity and in a more aqueous solvent system. One strategy to increase the strength of the interaction would be to provide additional binding contacts between the receptor and the helical peptide. Herein we report the combination of ion pairing and cation– $\pi$  interactions projected from a helical surface to enhance the affinity of the synthetic receptor for the peptide. This approach represents an example of de novo design of a protein surface where the properties of the surface of a protein (in this case the helical peptide) are modified to optimize binding to a target molecule.

The design of the peptide sequences exploited a “molecular hinge” strategy that we had used earlier in synthetic receptors for nucleotide bases.<sup>[6, 7]</sup> In this approach acylaminopyridine and naphthalene groups were linked to provide binding through hydrogen-bonding and  $\pi$ -stacking interactions (Scheme 1 A). In this current research our target peptides incorporate four aspartate groups, each flanked above or below by aromatic residues on the helix surface. In this way the tetraguanidinium receptor can potentially make both hydrogen-bonding and cation– $\pi$  contacts<sup>[8]</sup> with side-chain groups on the peptide (Scheme 1 B).<sup>[9, 10]</sup>

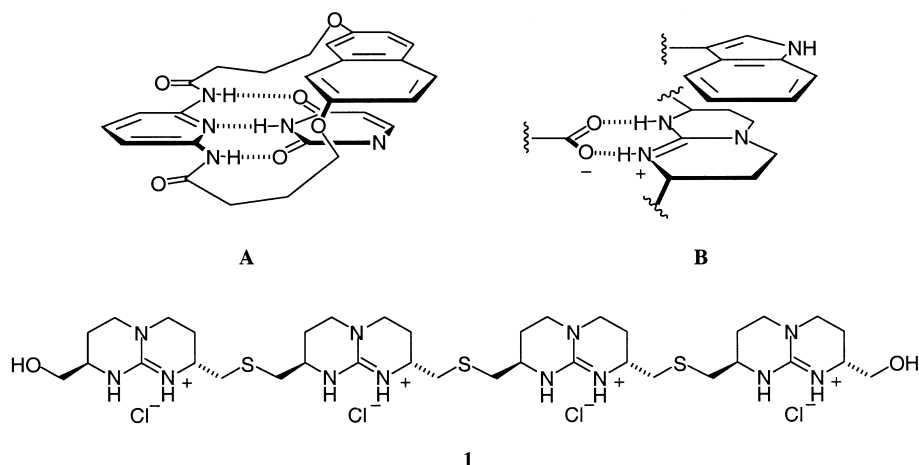
Three peptides were synthesized with four aspartic acid residues in the  $i, i+3$  relationship that has been shown to be

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Scheme 1. A) Molecular hinge design for the recognition of a nucleotide base.<sup>[6]</sup> B) Postulated binding geometry of the guanidinium binding site formed from a proximal aspartate and tryptophan group on an  $\alpha$ -helical surface.

required for optimal binding to receptor **1**.<sup>[4,5]</sup> In peptides **2** and **3**, Phe and Trp residues, respectively, were placed on the C-terminus side of each Asp residue in the sequence, while in peptide **4** the placement of the Asp and Trp residues was switched (Figure 1). Binding comparisons were made to a control peptide, **JV4**, which contains four aspartate residues but no flanking aromatic residues.

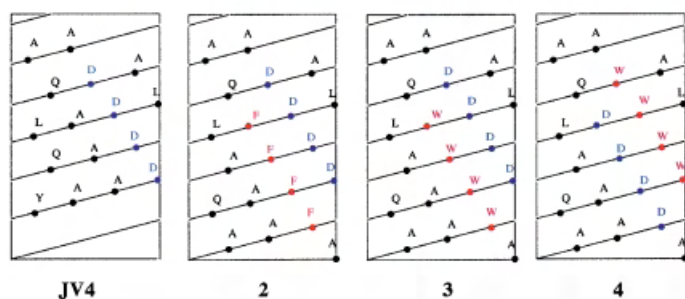
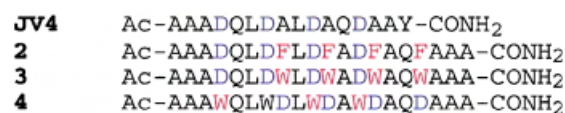


Figure 1. Sequences and helix net diagrams of synthesized peptides.

Binding studies on receptor **1** with peptide **4** in 1:1 trifluoroethanol (TFE):water by CD spectroscopy showed a large increase in the helical character of the peptide (from 13 to 51 %) with one equivalent of **1**. Since the internal aromatic residues<sup>[11, 12]</sup> contributed to the CD signal, a more accurate analysis of helicity was attempted using NMR spectroscopy (see below).<sup>[13]</sup> The binding isotherm obtained by CD analysis pointed to an interaction too strong to measure accurately.<sup>[14]</sup> Titrations monitored by the fluorescence of the Trp residue, however, allowed the use of lower concentrations and an affinity constant of  $1.1 \times 10^8 \text{ M}^{-1}$  was measured (Table 1). Dilution experiments and Job analysis confirmed that the peptide does not aggregate at relevant concentrations and the stoichiometry of the complex is 1:1. The relative position of the Asp and Trp residues is clearly important since the binding

Table 1. Binding constants of **1** with various peptides in 1:1 TFE:water at 25 °C.

| Peptide    | Binding constant [ $\text{M}^{-1}$ ] |
|------------|--------------------------------------|
| <b>JV4</b> | $3.2 \times 10^6$                    |
| <b>2</b>   | $3.8 \times 10^6$                    |
| <b>3</b>   | $4.2 \times 10^6$                    |
| <b>4</b>   | $1.1 \times 10^8$                    |

of **1** to peptide **3** was 100-fold weaker (association constant of about  $10^6 \text{ M}^{-1}$ ) than to **4**. This  $K_a$  value is comparable to that of **1** and **JV4** ( $3.2 \times 10^6 \text{ M}^{-1}$ ) where no aromatic residues are available for cation- $\pi$  interactions and suggests that the Trp residues in **3** do not participate in binding. Similarly, the Phe residues in peptide **2** do not enhance binding ( $K_a = 3.8 \times 10^6 \text{ M}^{-1}$ ) in 1:1 TFE:water.

A comparison of the chemical shifts of the side-chain protons in the free peptide and in the complex helped to determine which side chains are in contact with the receptor (Figure 2). The diastereotopic  $\beta$  protons of the Asp and Trp side chains in the free peptide have degenerate chemical shifts as a consequence of rapid rotation around the  $\chi^1$  and  $\chi^2$  dihedral angles of the side chain. However, these resonances are strongly anisochronous in the complex and are indicative of restricted motion of the side chains through the establishment of noncovalent interactions with **1**.<sup>[4]</sup>

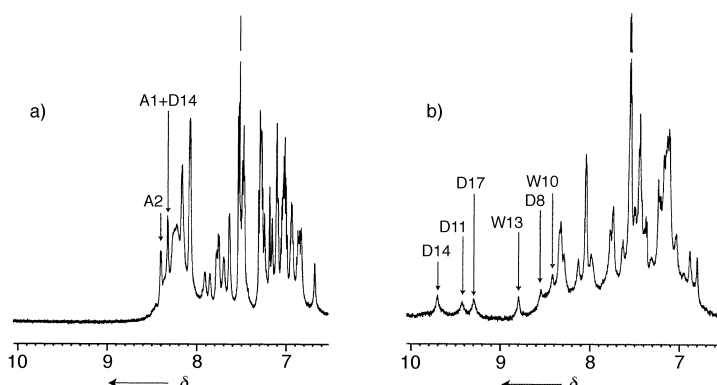


Figure 2. 1D  $^1\text{H}$  NMR spectra (Bruker DMX, 600 MHz,  $\text{CD}_3\text{OH}:\text{H}_2\text{O}$  (9:1), 278 K) of **4** (a) and complex **4:1** (b). The labels correspond to those residues with downfield-shifted NH resonances.

Analysis of NOE data and  $\alpha\text{H}$  secondary chemical shifts showed peptide **4** to have nascent helical secondary structure in only the first ten residues. Interaction with the receptor, however, caused a dramatic amplification of helicity in the rest of the sequence, as seen by the increase in the intensity and number of N-N ( $i, i+1$ ) and nonsequential N-N ( $i, i+2$ ) NOE interactions, characteristic of helical peptides,<sup>[15]</sup> which in the complex are present all along the sequence of the peptide.

Conclusive evidence for helix stabilization as a consequence of recognition is provided by changes in the secondary shifts of the NH protons (Figure 2). NH secondary shifts

( $\Delta\delta_{\text{NH}} = \delta_{\text{NH}}(\text{experimental}) - \delta_{\text{NH}}(\text{random coil})^{[15]}$ ) are related to the length of the hydrogen bond between the NH group at position  $i$  and the CO group of the residue at  $i - 4$  in helical peptides. A periodic trend in  $\Delta\delta_{\text{NH}}$  values which is observed for the complex (Figure 3) formed between **4** and **1** is typical

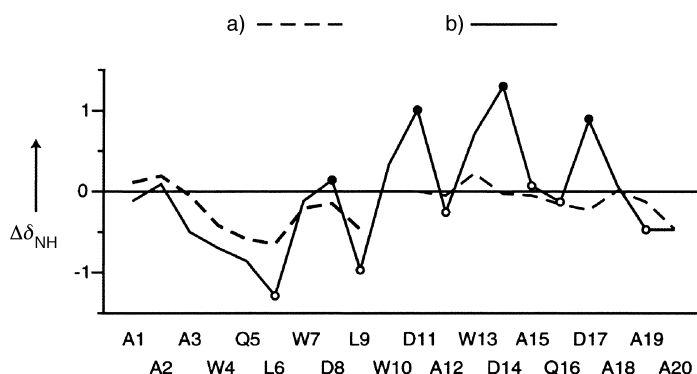


Figure 3. Secondary chemical shifts (NH) as a function of sequence for **4** (a) and complex **4:1** (b). Receptor-bound residues on the concave face of the helix are labeled with filled circles and those on the convex face with open circles.

of bent helices,<sup>[16]</sup> where the hydrogen bonds formed by residues on the convex face of the helix are shorter and cause a downfield shift of the NH protons involved. The residues exhibiting higher values of  $\Delta\delta_{\text{NH}}$  are those that interact with **1** which suggests that the helix is bent towards the receptor for optimal interaction.

The 30-fold difference in affinity between **3** and **4** for **1** clearly suggests that the participation of the Trp residues in binding is dependent on their position along the helix. Both **3** and **4** have similar initial helicities; therefore, conformational bias cannot be the origin of the differential binding. Changes in the pKa values of the Asp groups<sup>[17]</sup> as a result of their different positions with respect to the helix dipole are unlikely to be important. The closer proximity of the Asp groups to the C-terminus in **4** would be expected to lead to a decrease in affinity, not the increase in binding strength that is seen. Molecular modeling studies<sup>[17]</sup> of the relative position of the Asp and Trp side chains along the helix surface provide an explanation. In peptide **3** the indole groups are staggered relative to the aspartate residues and achieve little overlap with the guanidinium binding regions even when the  $\chi^2$  bonds of the Trp residues are rotated to a more binding-favorable orientation (Figure 4a and b).<sup>[18]</sup> In contrast, the aromatic side chains in peptide **4** can easily adopt a conformation that places the indole groups within stacking distance of the bound cations (Figure 4).

The interaction of **4** and **1** was also investigated in 100% water. An increase in the fluorescence emission of the Trp group in **1** that reached saturation at approximately one equivalent of **4** suggested strong binding. However, at higher concentrations of **4** aggregation effects became more prominent and precluded quantitative analysis of the binding.

In summary, we have designed a short  $\alpha$ -helix as a model protein surface for the recognition of a small molecule by cation- $\pi$  interactions. The peptide receptor not only binds

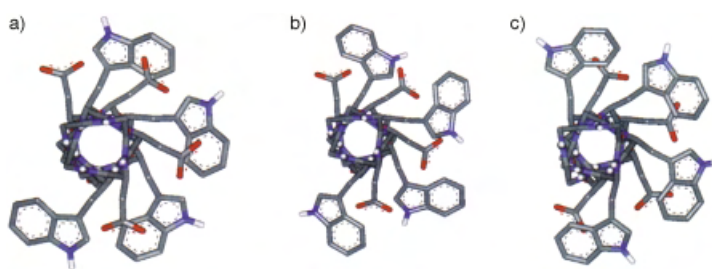


Figure 4. Comparison of the overlap of Trp and Asp side chains in the binding sites of **3** with the preferred side-chain conformations (a), **3** with the bond between the Trp  $\beta$  and  $\gamma$  carbon atoms rotated 180° (b), and **4** with the preferred side-chain conformation (c). All views are down the helix axis from the N-terminus and nonessential side chains are eliminated for clarity.

with high affinity but also acts to strongly stabilize the helix conformation of the peptide.

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# Cesiumauride Ammonia (1/1), $\text{CsAu} \cdot \text{NH}_3$ : A Crystalline Analogue to Alkali Metals Dissolved in Ammonia?\*

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Relativistic contributions to the energy of the electronic states in atoms grow with increasing atomic number, and become comparable to the usual shell structure effects beyond the fifth period. One of the consequences for the electronic structures is the relativistic radial contraction and energetic stabilization of the s shells which has been found to be most pronounced for gold.<sup>[1]</sup> Many of the peculiarities in the chemical and physical properties of gold can be traced back directly to this fact. Among others, this holds true for the high electron affinity (the highest of any metal) which explains the propensity of gold to adopt the negative oxidation state  $-1$ . By spectroscopic and, even more convincingly, chemical means it has been shown that this is not a barely formal valence state, but instead true ionic  $\text{Au}^-$  entities are present, when an appropriate environment is provided. In particular, the formation of the ternary phase  $\text{Cs}_3\text{AuO}$  from  $\text{CsAu}$  and  $\text{Cs}_2\text{O}$  by interdiffusion in the solid state has given conclusive support to this view.<sup>[2]</sup> To provide further evidence for  $\text{Au}^-$  ions being a stable species we have subject  $\text{CsAu}$  to an electrolytic dissociation by dissolving it in a polar solvent. Indeed,  $\text{CsAu}$  dissolves readily in liquid ammonia forming a yellow solution. Surprisingly, on slowly removing ammonia,  $\text{CsAu}$  was not recovered directly, instead a new, intense blue solid crystallized; with X-ray single-crystal data the structure

was solved and refined, and gave the composition  $\text{CsAu} \cdot \text{NH}_3$ . As the color is reminiscent of the blue solutions of alkali metals in ammonia,<sup>[3]</sup> and as gold( $-1$ ) can transfer electron density towards a suitable acceptor,<sup>[4]</sup> one could suspect this ammoniate to represent a crystalline analogue to the former electrode solutions.

The properties of cesiumauride ammonia (1/1),  $\text{CsAu} \cdot \text{NH}_3$ , are governed both by its highly reductive power and its thermal lability. In consequence, the compound is extremely sensitive towards even traces of water or oxidizing agents, for example, atmospheric oxygen. According to thermal analyses (simultaneous differential thermal analysis (DTA) and thermogravimetry (TG)),  $\text{CsAu} \cdot \text{NH}_3$  releases ammonia when heated above  $225 \pm 5$  K. Thus, the temperature of decomposition is well below the boiling point of ammonia (239 K) which indicates a moderate interaction of ammonia in the solid. An observed weight loss of 5 % agrees well with the assumed evolution of one mole of  $\text{NH}_3$  per mole  $\text{CsAu} \cdot \text{NH}_3$ .

The crystal structure of  $\text{CsAu} \cdot \text{NH}_3$ <sup>[5]</sup> exhibits features characteristic for low-dimensional systems. Slabs of overall composition  $\text{CsAu}$  are separated by single  $\text{NH}_3$  layers. The heavy-atom substructure can be derived from the structure of solvent-free  $\text{CsAu}$  by cutting out slabs oriented parallel to the crystallographic (110) direction, (Figure 1, left). These two-dimensional units have a thickness of half the unit-cell face diagonal and are separated by  $\text{NH}_3$  units. A similar structural motif is found in auride aurates, such as  $\text{Cs}_7\text{Au}_5\text{O}_2$ , where the same types of slabs are intercalated by  $\text{AuO}_2^{3-}$  entities.<sup>[6]</sup> In  $\text{CsAu} \cdot \text{NH}_3$  the gold atoms are shifted towards each other forming zigzag chains with comparatively short Au–Au separations ( $d(\text{Au}–\text{Au}) = 302$  pm, c.f.  $\text{CsAu}$ :  $d(\text{Au}–\text{Au}) = 426$  pm,<sup>[7, 8]</sup> Table 1), which indicates some bonding interac-

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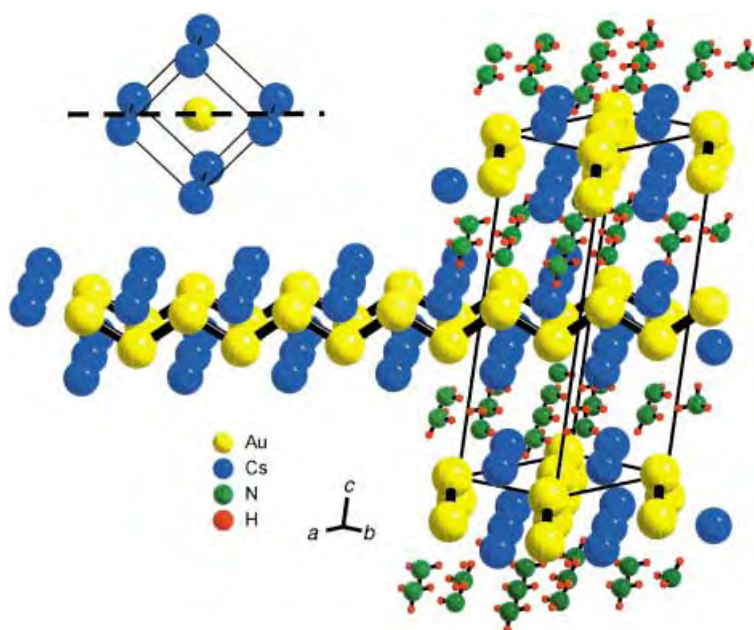


Figure 1. Structure of  $\text{CsAu} \cdot \text{NH}_3$ . Right: Unit cell. Left: Derivation of the  $\text{CsAu}$  substructure in  $\text{CsAu} \cdot \text{NH}_3$  from  $\text{CsAu}$ .  $\text{CsAu}$ , elemental cube (top).  $\text{CsAu} \cdot \text{NH}_3$  heavy atom substructure (middle).



Table 1. Interatomic distances in CsAu · NH<sub>3</sub>.

|       | d [pm]   |       | d [pm]   |
|-------|----------|-------|----------|
| Au–Au | 301.5(8) | Cs–N  | 323(1)   |
|       | 302(1)   |       | 323(2)   |
| Au–Cs | 359(2)   | Cs–Au | 359(2)   |
|       | 359.7(9) |       | 359.7(9) |
|       | 363.2(1) |       | 363.2(1) |
|       | 363.3(1) |       | 363.3(1) |
|       | 371.7(9) |       | 371.7(9) |
|       | 371.7(8) |       | 371.7(8) |

tion. The chains are well separated ( $d(\text{Au–Au, interchain}) = 504$  pm). The interatomic Cs–Cs distances are elongated ( $d(\text{Cs–Cs}) = 479$  pm, c.f. CsAu:  $d(\text{Cs–Cs}) = 426$  pm<sup>[7, 8]</sup>), while the mean Cs–Au separation ( $d(\text{Cs–Au}) = 365$  pm) is just slightly below the value found in CsAu ( $d(\text{Cs–Au}) = 369$  pm), Table 1.

Ammonia completes the coordination spheres of the heavy atoms in a way that for both Cs and Au the coordination number (C.N.) of 8 is restored (Figure 2a, b). Each NH<sub>3</sub> bridges two cesium atoms, forming an angle (Cs–NH<sub>3</sub>–Cs) of

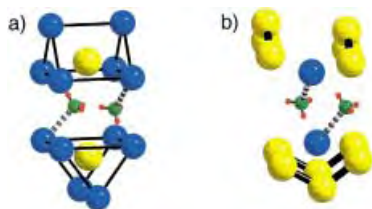


Figure 2. Au (a) and Cs (b) environments in CsAu · NH<sub>3</sub>. For color code see Figure 1.

94.73°. The NH<sub>3</sub> lone pair is directed to one of the Cs atoms and, in consequence, it is no longer available for hydrogen bonding. The Cs–N separation of 323 pm is comparable to those found for cesium ammoniates, for example, the polyphosphides.<sup>[9]</sup>

The title compound, which can be regarded as an ammoniate of an alloy, is without precedence from a chemical as well as a structural point of view. Thus, no reference systems are available which could serve as a basis for an attempt to understand and classify the properties and their relations to chemical bonding, and further experimental and theoretical work appeared to be necessary to gain insight into the electronic structure of this solid.

A particularly strong tool for probing the 6s electron concentration and distribution, which are assumed to play a key role, is <sup>197</sup>Au Mössbauer spectroscopy. The results give unambiguous evidence for a significant reduction of the electron density at the gold nucleus, as compared to the parent CsAu (Table 2). Taking into account the chemical shift only, the values for CsAu · NH<sub>3</sub> lie between those of RbAu and KAu<sub>2</sub>. The modest quadrupole splitting is attributed to the reduced symmetry at the gold site.<sup>[10]</sup>

Complementary information regarding the electronic structure of CsAu · NH<sub>3</sub>, as obtained by <sup>1</sup>H and <sup>133</sup>Cs NMR spectroscopic measurements. NMR spectroscopic data is available on the parent compounds, namely NH<sub>3</sub><sup>[11]</sup> and

Table 2. Mössbauer parameters of aurides.

|                        | Chemical shift $\delta$<br>[mm s <sup>-1</sup> ] | Quadrupole split $\Delta$<br>[mm s <sup>-1</sup> ] | FWHM<br>[mm s <sup>-1</sup> ] <sup>[a]</sup> |
|------------------------|--------------------------------------------------|----------------------------------------------------|----------------------------------------------|
| CsAu · NH <sub>3</sub> | 5.96(1)                                          | 1.75(2)                                            | 1.08(2)                                      |
| Au (reference)         | –1.23                                            | 0                                                  | 0.95                                         |
| KAu <sub>2</sub>       | 3.16(3)                                          | 4.23(4)                                            | 0.73(7)                                      |
| RbAu                   | 6.70(2)                                          | 0                                                  | 1.31(5)                                      |
| CsAu                   | 7.00(2)                                          | 0                                                  | 0.96(6)                                      |

[a] FWHM = full width at half maximum.

CsAu,<sup>[12–14]</sup> on various solutions of alkali metals in ammonia,<sup>[15, 16]</sup> and other materials with localized charge inhomogeneities.<sup>[17]</sup>

Here we report <sup>1</sup>H (100 MHz, TMS) and <sup>133</sup>Cs (50 MHz, CsNO<sub>3</sub>) NMR spectroscopy performed on CsAu · NH<sub>3</sub> powder samples as well as <sup>1</sup>H NMR spectroscopy on pure ammonia and <sup>133</sup>Cs NMR spectroscopy on CsAu. We have used a home-built pulsed NMR spectrometer and measured spectral lineshapes as well as spin-lattice relaxation rates for temperatures below 200 K down to 5 K.

The <sup>1</sup>H line position, linewidth, and spin-lattice relaxation suggest that the properties of solid ammonia are essentially preserved in CsAu · NH<sub>3</sub>. The dynamics of the ammonia molecules can be described in a way similar to those of pure solid NH<sub>3</sub>.<sup>[11]</sup> The molecules undergo a hindered rotation around their symmetry axis with an activation energy of about 100 meV (4800 kJ mol<sup>-1</sup>) and a correlation time  $\tau_c^0$  of  $3.7 \times 10^{-13}$  s. Above 180 K a sizable narrowing of the <sup>1</sup>H resonance line occurs within a small temperature range of about 5 K. Since this temperature is very close to the melting temperature of pure ammonia we attribute the observed line narrowing to a melting transition in the NH<sub>3</sub> layers.

The <sup>133</sup>Cs spectra (Figure 3) for 86 K display a strongly broadened and asymmetrical lineshape with a high-frequency tail which is not observed in pure CsAu. The latter shows a

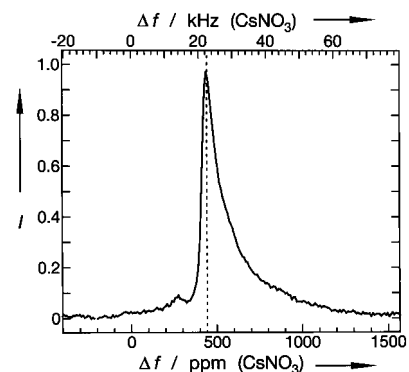


Figure 3. <sup>133</sup>Cs NMR spectrum of CsAu · NH<sub>3</sub> at 86 K. The dashed line marks the line position of pure CsAu which exhibits a chemical shift of ca. 420 ppm. The reference is an aqueous 1M CsNO<sub>3</sub> solution.

much narrower, symmetric resonance signal with only a weak temperature dependence between 80 K and 350 K. The frequency of the maximum spectral intensity in CsAu · NH<sub>3</sub> coincides with the spectral line position of CsAu for temperatures between 80 K and 200 K (dashed line in Figure 3). The line broadening clearly is inhomogeneous in character since

the spin-lattice relaxation rates vary over the signal, being sizably enhanced for Cs nuclei showing a large frequency shift. The behavior of both, lineshape and relaxation, can be explained by assuming dilute localized inhomogeneities in electron density on the CsAu chains which induce an additional site-dependent frequency shift and an enhanced fluctuation strength. We note here that the line is not “Knight-shifted” since there is no paramagnetism observed neither in magnetic susceptibility nor in ESR measurements. The observed shift is a result of the chemical shift, which in the case of  $^{133}\text{Cs}$  is on the order of 15000 ppm.<sup>[12, 13, 18]</sup> The origin of the observed localized inhomogeneities can be attributed to a reduction of the charge density in the Au partial structure by a charge transfer towards the cesium/ammonia regions. Assuming a bipolaron state of spin-paired electrons (charge  $2e^-$ , spin  $S=0$ ) would explain both the observed NMR spectroscopic behavior of the Cs centers and the diamagnetism of the bulk samples as determined by superconducting quantum interference device (SQUID) measurements. The electron is distributed over several  $\text{NH}_3$  molecules. The charge transfer refers to only a few percent of an electron per Au center. The corresponding bipolarons are either randomly distributed or somewhat ordered. This cannot be distinguished at the moment. In any case it leads to a distribution of the chemical shifts of the  $^{133}\text{Cs}$  signal as will be elaborated in a separate publication. We note that the effect of a localized charge on NMR spectrum parameters is substantially enhanced for  $^{133}\text{Cs}$  nuclei in comparison with  $^1\text{H}$  nuclei since the former exhibits large chemical-shift changes induced by the electronic environment a result of an easily polarizable electron shell.<sup>[18]</sup>

This way of explaining the experimental results is backed in part by an electronic-structure calculation of  $\text{CsAu} \cdot \text{NH}_3$ , and, for comparison, of the related compound  $\text{CsAu}$ . We use the density functional theory (DFT) in the local density approximation (LDA).<sup>[19]</sup> For both compounds the internal atomic coordinates were fixed from the experiments and the volume was allowed to vary. The electronic gap between empty and occupied states is a similar value in both compounds, a trend that is likely to be true in spite of the LDA errors. The character of the states at the top of the valence band (HOMO) and at the bottom of the conduction band (LUMO) is shown in Figure 4. In both  $\text{CsAu}$  (Figure 4a) and  $\text{CsAu} \cdot \text{NH}_3$  (Figure 4b) the top of the valence band is a state which is mostly localized on the Au atoms. In contrast the bottom conduction state is located in the interstitial region in  $\text{CsAu}$  and on the N atom in  $\text{CsAu} \cdot \text{NH}_3$ .

Further insight into the bonding properties of these compounds can be extracted from the maximally localized Wannier functions.<sup>[20]</sup> The spread of the resulting Wannier functions and their Kohn and Sham Hamiltonian expectation value ( $\langle w_i | H | w_i \rangle$ ) are shown in Table 3. For  $\text{CsAu}$  it turns out that the valence electrons are localized on the gold atom, totally in line with the accepted picture of  $\text{CsAu}$  as an almost ionic compound, where, because of the difference in electronegativity the Cs electron is transferred to the gold atom. The doubly occupied valence states can be partitioned into two groups; two representative Wannier functions are shown in Figure 5 and exhibit a clear s+d character.

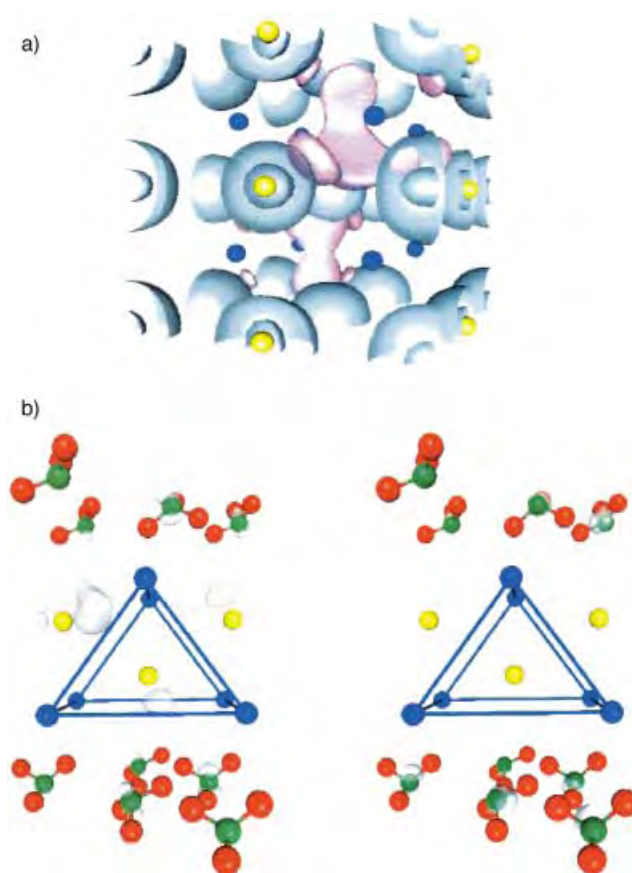


Figure 4. a) HOMO (blue) and LUMO (rose) states of  $\text{CsAu}$ . b) HOMO (left) and LUMO (right) states of  $\text{CsAu} \cdot \text{NH}_3$ . For color code see Figure 1.

Table 3. Spread in real space and average energy of the Wannier functions located over a gold atom in  $\text{CsAu} \cdot \text{NH}_3$  and  $\text{CsAu}$ .

| State | $\text{CsAu} \cdot \text{NH}_3$ |                                              | $\text{CsAu}$                 |                                              |
|-------|---------------------------------|----------------------------------------------|-------------------------------|----------------------------------------------|
|       | $S [\text{\AA}]^{\text{[a]}}$   | $\langle E \rangle [\text{eV}]^{\text{[b]}}$ | $S [\text{\AA}]^{\text{[a]}}$ | $\langle E \rangle [\text{eV}]^{\text{[b]}}$ |
| a     | 0.704                           | − 5.996                                      | 0.705                         | − 7.943                                      |
| b     | 0.712                           | − 5.965                                      | 0.705                         | − 7.943                                      |
| c     | 0.719                           | − 5.831                                      | 0.705                         | − 7.943                                      |
| d     | 0.720                           | − 5.825                                      | 0.770                         | − 7.775                                      |
| e     | 0.726                           | − 5.734                                      | 0.770                         | − 7.775                                      |
| f     | 0.965                           | − 5.578                                      | 0.770                         | − 7.775                                      |

[a]  $S = \sum_i (\langle w_i | r^2 | w_i \rangle - \langle w_i | r | w_i \rangle^2)$ . [b]  $\langle E \rangle = \langle w_i | H | w_i \rangle$ .

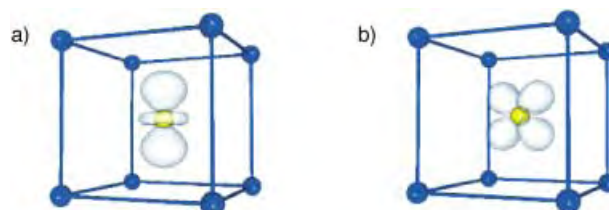


Figure 5. Wannier densities of  $\text{CsAu}$ . a) Lower energy set of degenerate Wannier states. b) Higher energy set. For color code see Figure 1.

$\text{CsAu} \cdot \text{NH}_3$ , in contrast, no longer shows degenerate Wannier functions as a result of the much lower symmetry. The lowest five Wannier functions maintain the character they had in the parent compound, albeit distortion occurs because of the lowering in symmetry as exemplified in Figure 6a, b. Wannier

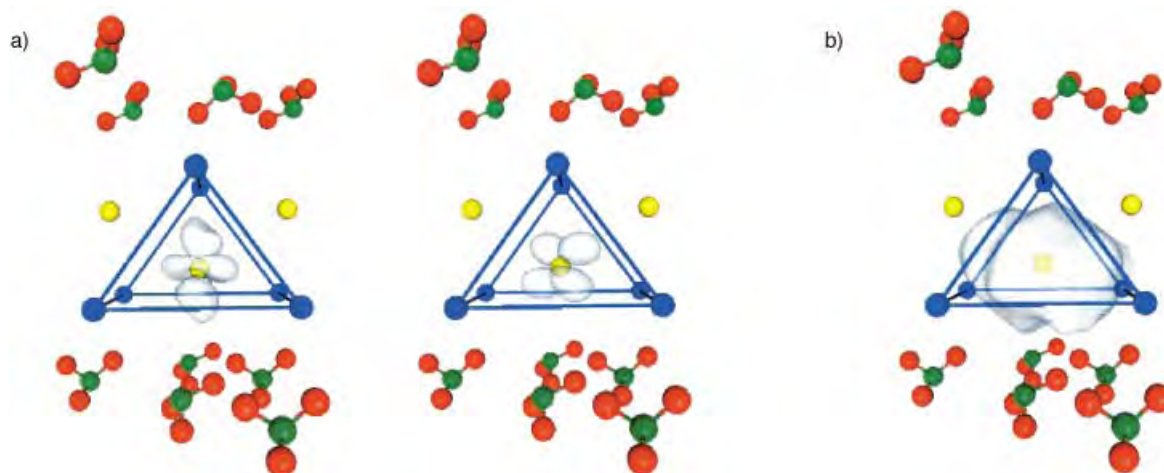


Figure 6. Densities of Wannier states of  $\text{CsAu} \cdot \text{NH}_3$ . a) Two representatives of the lowest five Wannier functions which maintain the s+d character they had in  $\text{CsAu}$ . b) High-energy Wannier function losing the d character and resembling more a distorted s state. For color code see Figure 1.

function six, on the other hand, which is the highest in energy, is substantially changed; its spread is significantly larger and its center is slightly shifted from the gold atom by  $0.108 \text{ \AA}$  in the direction of the nearest ammonia layer, losing the d character and resembling a slightly distorted s state. We believe that it is this particular state which is responsible for many of the properties of  $\text{CsAu} \cdot \text{NH}_3$ . However, this static calculation cannot shed any light on the nature of the bipolaronic states as suggested by the NMR spectrometry results.

In summary, the intercalation of ammonia (in a formal sense) into  $\text{CsAu}$  reduces the coulomb field exerted by the cesium ions on the gold centers, which destabilizes the negatively charged state. As a consequence some electron density is removed from the gold site. This picture is in accordance with all the experimental findings, as there are formation of (weak) gold–gold bonds, shift of the Mössbauer signal, and broadening and shift of the NMR signal of the Cs centers.

### Experimental Section

All manipulations were carried out either under dry argon, in vacuum, or under an atmosphere of ammonia. Ammonia (Bayer AG, Leverkusen, Germany) was made anhydrous by condensing it first on sodium, then on potassium, where it was stored as a potassium–ammonia solution at 195 K until usage. Cesiumauride was synthesized directly from the elements at 493 K by using an excess of alkali metal which was distilled off in the dynamic vacuum of a mechanical oil pump on completion of the reaction. Cesium was gained by reducing its chloride with calcium<sup>[21]</sup> and further purified by twofold distillation under vacuum. Elemental gold was precipitated by reducing tetrachloric gold acid with sodium oxalate.<sup>[22]</sup>

In an H-shaped all-glass reaction vessel with its two legs separated in the middle by a glass frit (porosity 2),  $\text{CsAu}$  was placed on the one side and liquid ammonia was condensed onto it (at  $T = 175 \text{ K}$ ). The  $\text{CsAu}$  was dissolved by warming to the boiling point of ammonia, then the solution was poured through the glass frit. Upon slow evaporation of the solvent intense blue colored crystals of  $\text{CsAu} \cdot \text{NH}_3$  precipitated—which evolved ammonia, after the solvent was removed, at  $225 \pm 5 \text{ K}$ . This procedure was repeated until all the  $\text{CsAu}$  was recrystallized.

For selecting and mounting single crystals we have adapted the technique described by Kottke and Stalke.<sup>[23]</sup> For all other analytical investigations the ammoniate was synthesized from  $\text{CsAu}$  and  $\text{NH}_3$  directly in the respective

silica sample containers which were sealed under vacuum (the samples were cooled in liquid nitrogen during this procedure to prevent decomposition).

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## High-Throughput Screening of Enantioselective Catalysts by Immunoassay

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Interest is continuously growing in the application of powerful combinatorial approaches to the discovery of new catalysts by combining synthesis and screening of large libraries.<sup>[1]</sup> Although this area is still in its infancy, several catalysts have already been identified by parallel synthesis

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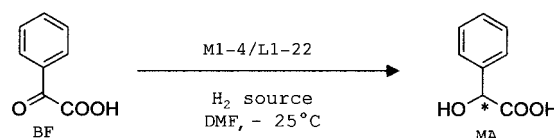
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Supporting information for this article is available on the WWW under <http://www.angewandte.com/> or from the author.

and high-throughput-screening (HTS) techniques.<sup>[2]</sup> However, the factor limiting an efficient extension of this research to asymmetric catalysis remains the lack of efficient methods for rapid screening of enantioselective reactions.<sup>[3]</sup> To overcome this major obstacle, a first approach consists in screening the catalyst library for activity using an HTS procedure and then testing each lead for enantioselectivity by conventional methods,<sup>[4]</sup> but this is only amenable if few catalysts from the broad library are active. Clearly, a high-throughput technique allowing quantification of both activity and enantioselectivity would accelerate the rate at which asymmetric catalysts are discovered. Recently, IR thermography,<sup>[5]</sup> capillary array electrophoresis,<sup>[6]</sup> CD-HPLC,<sup>[2c]</sup> and electrospray ionization based on the use of isotopically labeled substrates<sup>[7]</sup> have emerged as promising but equipment-intensive techniques for the screening of enantioselective catalysts.<sup>[8]</sup>

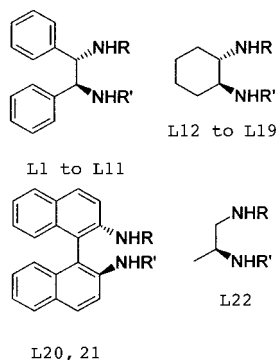
Herein, we describe a new HTS method for the simultaneous screening of multiple catalysts for the enantioselective reduction of ketones. This procedure, allows quantification of both yields and enantiomeric excess (*ee*) in an HTS format using inexpensive and commonly available equipment.

Our interest in this field was focused on the enantioselective reduction of  $\alpha$ -keto acids by hydrogen transfer using chiral metal complexes. Although considerable effort was expended to develop applicable methods for the enantioselective preparation of  $\alpha$ -hydroxy acids,<sup>[9]</sup> only a few papers<sup>[10]</sup> are devoted to the development of straightforward procedures involving the direct conversion of  $\alpha$ -keto acids to chiral  $\alpha$ -hydroxy acids. As a model reaction, we chose the enantioselective reduction of benzoyl formic acid (BF) into mandelic acid (MA). The catalyst library was prepared by combining a set of 22 chiral diamine-based ligands and four different metal species (Scheme 1).



Metal library:  
M1 : [RuCl<sub>2</sub>(*p*-cym)<sub>2</sub>]  
M2 : [RuCl<sub>2</sub>(benz)<sub>2</sub>]  
M3 : [RhCl<sub>2</sub>(Cp)<sub>2</sub>]  
M4 : [IrCl<sub>2</sub>(Cp)<sub>2</sub>]

Ligand library:



| L  | R                                                                     | R'                                                              |
|----|-----------------------------------------------------------------------|-----------------------------------------------------------------|
| 1  | H                                                                     | H                                                               |
| 2  | CF <sub>3</sub> SO <sub>2</sub>                                       | H                                                               |
| 3  | C <sub>6</sub> F <sub>5</sub> SO <sub>2</sub>                         | H                                                               |
| 4  | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>       | H                                                               |
| 5  | 2, 4, 6-CH <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> | H                                                               |
| 6  | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>       | H                                                               |
| 7  | C <sub>6</sub> F <sub>5</sub> SO <sub>2</sub>                         | H                                                               |
| 8  | CF <sub>3</sub> CO                                                    | H                                                               |
| 9  | C <sub>6</sub> H <sub>5</sub> CO                                      | H                                                               |
| 10 | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>       | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> |
| 11 | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CO <sub>2</sub>         | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CO <sub>2</sub>   |
| 12 | H                                                                     | H                                                               |
| 13 | CF <sub>3</sub> SO <sub>2</sub>                                       | H                                                               |
| 14 | C <sub>6</sub> F <sub>5</sub> SO <sub>2</sub>                         | H                                                               |
| 15 | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>       | H                                                               |
| 16 | 2, 4, 6-CH <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SO <sub>2</sub> | H                                                               |
| 17 | 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>       | H                                                               |
| 18 | CF <sub>3</sub> SO <sub>2</sub>                                       | CF <sub>3</sub> SO <sub>2</sub>                                 |
| 19 | CH <sub>3</sub> SO <sub>2</sub>                                       | CH <sub>3</sub> SO <sub>2</sub>                                 |
| 20 | H                                                                     | H                                                               |
| 21 | CF <sub>3</sub> SO <sub>2</sub>                                       | H                                                               |
| 22 | H                                                                     | H                                                               |

Scheme 1. Target reaction and catalyst library.



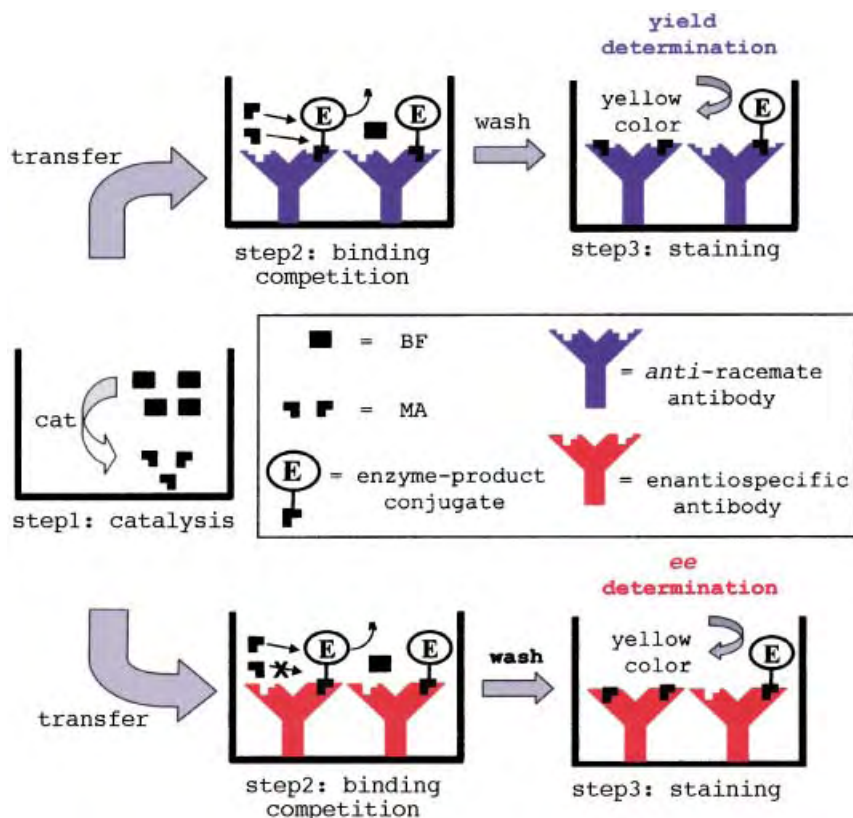


Figure 1. Schematic depiction of the HTS procedure using EIA.

For the screening of this library, we decided to use competitive enzyme immunoassays (EIA).<sup>[11]</sup> This powerful analytical method is based on the highly specific binding properties of antibodies which allow the direct measurement of the concentration of a given product in complex mixtures. Although EIA is widely used in the area of biology and diagnosis in particular, its application in the field of chemistry is not advanced. We envisioned that this analytical tool would be well adapted to measurement in an HTS format of both yield and enantiomeric excess of an enantioselective chemical transformation. By using an antibody that binds indiscriminately the two enantiomers of the product (MA for our model reaction) it should be possible to measure the concentration of the reaction product in the crude mixtures and thus to calculate the yield of the reactions. Determination of the enantiomeric excess would then be achieved by measuring the concentration of one enantiomer with an enantiospecific antibody. Thus, evaluation of one enantioselective catalyst will involve a three-phase procedure, the reaction itself and two jointly run EIA (Figure 1).

The crude catalyzed reaction mixture and a product-enzyme conjugate are added to a 96-well microtiter plate containing a specific *anti*-product antibody immobilized in the solid phase. Catalytic activity results in the formation of product that competes with the enzyme-product conjugate for antibody-binding sites. This leads to a decrease in absorbance (signal related to the solid-phase-bound enzyme activity), which is related to the concentration of product in the reaction mixture. With the use of simple and cheap

automated equipment (plate washer and plate absorbance reader), thousands of catalysts can be screened easily per day.

Antibodies with appropriate binding specificity are of critical importance for the elaboration of our HTS technique. Stereoselective interaction between enantiomers and monoclonal or polyclonal antibodies is well known<sup>[12]</sup> and has recently been used in various applications.<sup>[13]</sup> For this purpose, we used monoclonal antibodies (mAbs) raised against hapten H3 (a vanillin mandelic acid analogue) that tightly bind a broad range of molecules with an MA moiety, as we previously reported.<sup>[14]</sup> We found that among these antibodies, two mAbs have the properties mentioned above. mAb-15 is an antibody that binds the two enantiomers of MA (relative affinity for (*S*)-MA = 6.4 mM; (*R*)-MA = 7 mM as determined by EIA experiments) equally well, whereas mAb-8 exhibits high stereoselectivity toward (*S*)-MA (relative affinity for (*S*)-MA = 55  $\mu$ M, cross reactivity for (*R*)-MA < 0.1 %). Typical EIA calibration curves are presented in Figure 2.

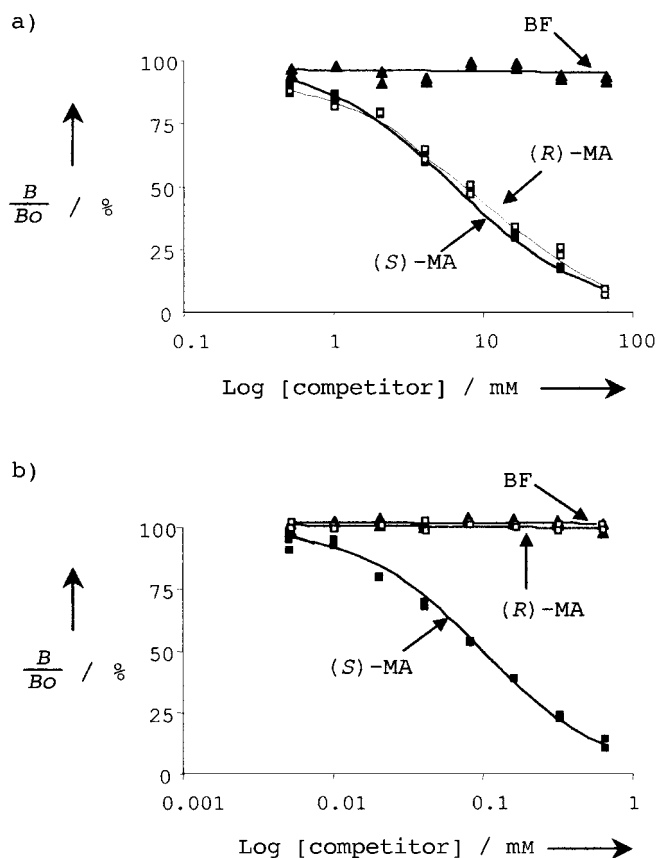


Figure 2. Antibody specificities. a) mAb-15; b) mAb-8. *B* and *B*<sub>0</sub> represent the bound enzyme activity measured in the presence and absence of competitor, respectively.

The ability of these mAbs to bind MA selectively allowed us to cover a large array of reaction conditions without any interference due to BF or to the catalyst library (cross-reactivities were less than 0.1%). Having these analytical tools in hand, we performed the HTS on our catalyst library. The latter was prepared by heating the metal precursors and the ligands in DMF. Two classical hydrogen sources (HCOOH/tetraethylammonium (TEA) and *i*PrOH/KOH) were used to achieve the catalyses in DMF. Each distinct combination was run in one well of a 96-well microtiter plate (see Supporting Information). This leads to 176 different reactions which were screened in a few hours using our HTS method. Representative results are shown in Figure 3.

To validate our technique, we compared EIA and HPLC values on 42 representative samples from the crude catalyzed reactions. Good correlation was obtained for EIA and HPLC analysis (Figure 4) although a fairly broad variation in enantiomeric excess was observed (the precision of the *ee* determination was evaluated at  $\pm 9\%$ , see Supporting Information). Linear regression analyses gave the following equations:  $EIA = 0.984 HPLC - 0.569$ ,  $r^2 = 0.971$ ,  $n = 42$  and  $EIA = 1.031 HPLC - 0.464$ ,  $r^2 = 0.932$ ,  $n = 42$  for the yield and *ee* determination, respectively.

From a chemical point of view, some general trends can be drawn from this screening: the best results were obtained with HCOOH/TEA as hydrogen source, NaOH/*i*PrOH gave less than 30% yields and poor *ee* values regardless of the catalyst used (results not shown). Thus, using HCOOH/TEA as hydrogen source, more than 50% of the catalysts were very efficient in terms of yield but only 5% of them gave an enantiomeric excess of over 60% *ee*, underlining the need for a screening method that allows determination of both yield and *ee*. The best catalyst identified by our HTS technique is a combination of M1 and L2 in DMF/HCOOH/TEA. Under

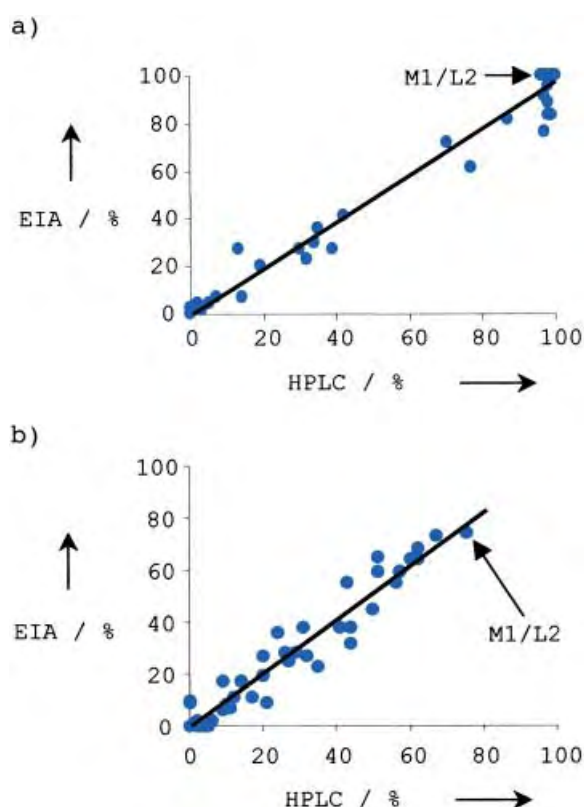


Figure 4. HPLC/EIA correlation. a) yields ; b) *ee* (S) values.

these conditions, the lead catalyst allows quantitative reduction of BF to MA with an enantiomeric excess of 81% *ee* (MA(S)). This result was confirmed by HPLC (yield = 98%; 79% *ee*) and reproduced on the mmol scale without significant decrease in yield or *ee*.

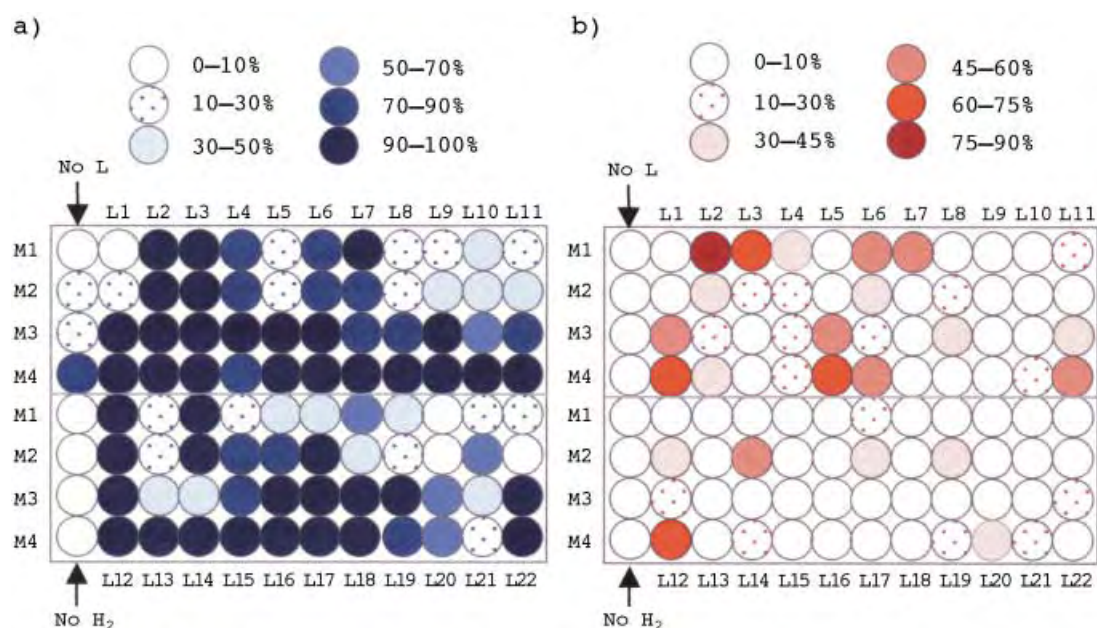


Figure 3. Screening of the catalyst library for the reduction of BF to (S)-MA. a) yields ; b) *ee* (S). Yields and *ee* values are presented in a color-coded format (blue for yields and red for *ee*). Catalyses were performed in DMF using HCOOH/TEA as hydrogen source and 1.6% of chiral catalyst (metal/ligand ratio 1:1.2 in DMF) at room temperature for 14 h. The control experiments without hydrogen source or without ligand are given in the left rows.

In conclusion, we have demonstrated the value of immunoassays for the development of highly efficient methods to screen enantioselective catalysts. The underlying principle of the procedure is general and should be successfully applied to any type of catalysis if one has antibodies with the required binding specificity. In fact, the immune system itself is a huge combinatorial machine providing a diverse set of specific binding molecules, and it is generally accepted that antibodies can be raised against virtually any compound of interest according to one's need. Furthermore, the use of antibodies for automated assays is routine and involves simple and time-saving experimental procedures. For these reasons, immunoassays appear to be effective ways of developing new high-throughput screening for the discovery of catalysts.

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## Ordered Langmuir–Blodgett Films of Amphiphilic $\beta$ -Hairpin Peptides Imaged by Atomic Force Microscopy\*\*

Evan T. Powers, Sung Ik Yang, Charles M. Lieber,\* and Jeffery W. Kelly\*

Langmuir and Langmuir–Blodgett (LB) films of peptides have a number of potential applications.<sup>[1–7]</sup> The fulfillment of this potential will depend on developing the molecular level understanding needed to control both the order within these films and their structures. Self-assembly in thin peptide films can be characterized by circular dichroism<sup>[8–10]</sup> and IR<sup>[11, 12]</sup> spectroscopies, fluorescence microscopy,<sup>[13–15]</sup> and at high resolution by grazing incidence X-ray diffraction (GIXD),<sup>[3, 14]</sup> and atomic force microscopy (AFM).<sup>[5, 16]</sup> Previous fluorescence microscopy results demonstrate that peptide **1** self-assembles into liquid- and solid-phase domains at the air–water (A–W) interface.<sup>[13]</sup> Here, we have used AFM with carbon nanotube tips to image LB films of **1** and its longer relative, **2**. The images show crystalline, two-dimensional order in films of **1** and **2** and demonstrate that the assembly parameters can be varied through well-defined changes in peptide structure.

The 14- and 18-residue peptides **1** and **2** both have a dPro-Gly sequence in the middle of alternating hydrophilic (Glu)

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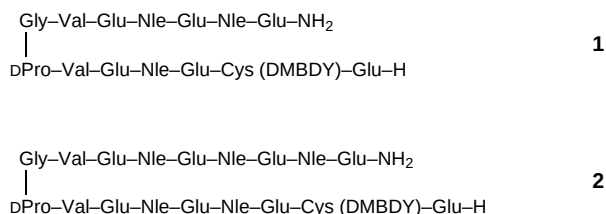
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and hydrophobic (Val, norleucine (Nle), labeled Cys) residues. The DPro-Gly sequence favors type II'  $\beta$ -turn conformations,<sup>[17, 18]</sup> while alternating hydrophilic/hydrophobic sequences at the A–W interface favor  $\beta$ -strand conformations,<sup>[2, 9, 19]</sup> making it likely that **1** and **2** will form amphiphilic  $\beta$ -hairpins at the A–W interface. The sole cysteines in **1** and **2** were labeled with the 5,7-dimethyl derivative of the BODIPY (Molecular Probes) fluorophore (DMBDY) for concentration determination.<sup>[13]</sup>

The surface pressure–molecular area ( $\Pi$ -A) isotherms in Figure 1 show that monolayers of **1** and **2** spread on deionized water (DIW) are stable although about 20% of **1** dissolves after spreading, consistent with its known water solubility.<sup>[13]</sup> The  $\Pi$ -A isotherm of **1** has been corrected to account for this

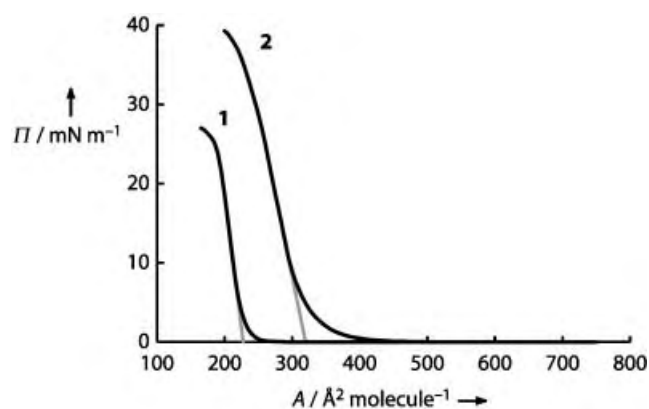


Figure 1. Black lines: Surface pressure–molecular area ( $\Pi$ -A) isotherms for **1** and **2** on DIW. Gray lines: extrapolations to the  $x$  axis from the points of steepest slope on the isotherms.

(see Supporting Information for details). Peptide **2** dissolves to a much lesser extent, so its  $\Pi$ -A isotherm is not corrected. The limiting molecular areas of **1** and **2**, obtained by extrapolation of the  $\Pi$ -A isotherm to the  $x$  axis,<sup>[20]</sup> are  $230 \text{ Å}^2 \text{ molecule}^{-1}$  for **1** and  $320 \text{ Å}^2 \text{ molecule}^{-1}$  for **2**.

Single layer LB films of **1** and **2** were deposited at  $10 \text{ mN m}^{-1}$  onto freshly cleaved mica (with the hydrophilic side of the monolayer facing the substrate and the hydrophobic side facing outward). The LB monolayers were then imaged by tapping mode AFM using single-wall carbon nanotube (SWNT) tips. SWNT tips have many advantages over Si tips, the most important here being reproducibly high lateral resolution.<sup>[21]</sup> This resolution is evident in Figure 2 and

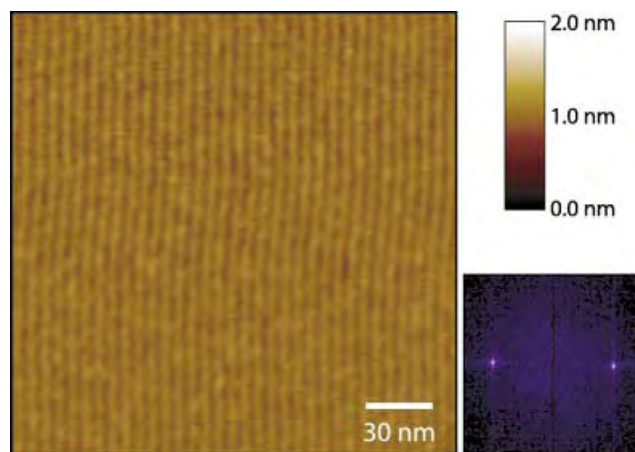


Figure 2. Left: AFM image of an LB monolayer of **1** deposited at  $10 \text{ mN m}^{-1}$  on mica. Right: height scale and Fourier transform of the image.

3, which show representative images of LB monolayers of **1** and **2**, respectively. Patterns of ridges with peak-to-trough heights of  $2\text{--}4 \text{ Å}$  are prominent in both Figure 2 and 3. Although similar features can be observed by using standard microfabricated tips, the SWNT tips enable lattice-resolved data to be obtained reproducibly without the need to search for a “good” tip. The repeat periods of the ridges can be determined from the images’ Fourier transforms (FT). There

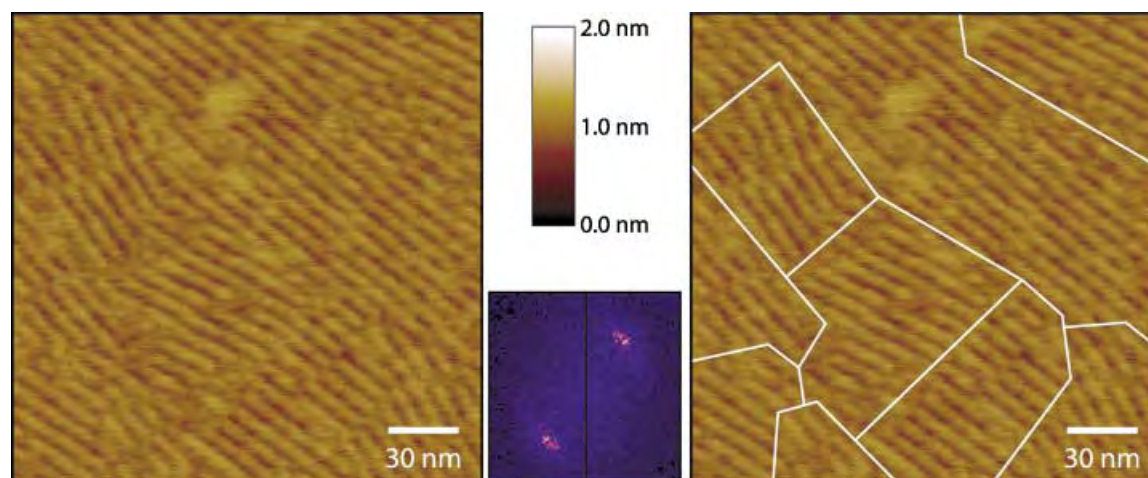


Figure 3. Left: AFM image of an LB monolayer of **2** deposited at  $10 \text{ mN m}^{-1}$  on mica. Middle: height scale and Fourier transform of the image. Right: Scan area divided into domains.

is only one set of parallel ridges in Figure 2, corresponding to a single maximum in the FT at 61 Å. In contrast, there are several domains of parallel ridges in Figure 3, corresponding to a radial streak in the FT at around 74 Å. The average ridge periods obtained from over 70 measurements each on LB monolayers of **1** and **2** are similar to those found above: 59(±1) Å for **1** and 74(±1) Å for **2**. The monolayer height, measured from holes in the films to the tops of the ridges, is 7(±1) Å.

Figure 2 vividly illustrates the crystallinity in monolayers of **1**. Here, a single domain extends for hundreds of nanometers in the directions parallel and perpendicular to the ridges. Images from larger scan areas (see Supporting Information) show that such domain sizes are typical for **1**, attesting to its strong propensity to assemble. The use of 1–2 nm diameter tips provides high confidence that defects are not being averaged out by the use of large contact area tips, and that the region shown is indeed virtually defect-free. Although defects such as grain boundaries appear in other images, LB monolayers of **1** are generally very well ordered.

Figure 3 demonstrates that the ridge period can be increased (from 59 Å to 74 Å) by adding residues to the peptide, while retaining a great deal of order in the monolayer. Although the domains outlined in Figure 3 are smaller than the one in Figure 2, they still persist for tens of nanometers. Images from larger scan areas (see Supporting Information) show that such sizes are typical. The effects on the assembly of the added residues in **2** (increased ridge period and decreased domain sizes) mirror the observations of Rapaport and co-

workers on peptide monolayers at the A–W interface.<sup>[3]</sup> They also found that the lattice spacing increased and monolayer order decreased with increasing peptide length. This correspondence suggests that a monolayer's state at the A–W interface directly influences the degree of order in LB films.

The features in these LB monolayers can only be fruitfully discussed in light of a structural model. Such a model for **1**, based on the high  $\beta$ -sheet content found previously in its LB monolayers<sup>[13]</sup> and the AFM images above, is illustrated in Figure 4. The assembly consists of  $\beta$ -hairpins of **1**, each 9.4 Å wide and 25 Å long (according to typical  $\beta$ -sheet dimensions<sup>[22]</sup>). These associate by hydrogen bonding in the direction perpendicular to the strands to form cross- $\beta$  sheets. These sheets have two interfaces: a polar one composed of the termini and a nonpolar one composed of the turns. They are assembled laterally along both interfaces, driven by electrostatic and van der Waals interactions, respectively. The expected monolayer height in this model is 7–10 Å depending on the side chain conformations, matching the observed height of 7 Å. Individual ridges correspond to pairs of cross- $\beta$  sheets assembled along their polar interfaces, making the expected ridge period 55 Å. This is within 7 % of the observed (59 Å) ridge period.

The model is supported by the match between the expected and observed ridge periods, but its further evaluation is complicated by the AFM images' providing only one lattice parameter, the ridge period, when three are required to define a two-dimensional unit cell. Other information can, however, be used to judge the model. For example, we note that by

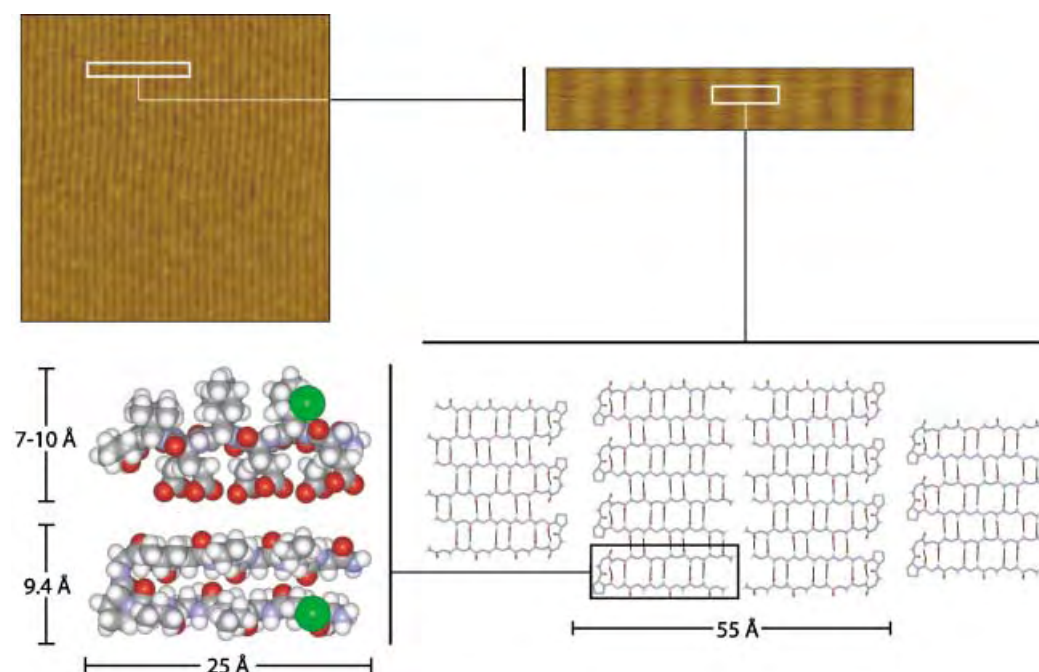


Figure 4. Molecular model for the assembly of **1**. The scan area from Figure 2 is shown in the top left. A white box encloses a small section of the scan area, which is expanded in the top right. Another white box in the expansion encloses a ridge with two flanking half-ridges. A molecular model for the assembly in the enclosed area is shown in the bottom right. The central ridge corresponds to the two central columns of  $\beta$ -hairpins, which interact with each other through their polar termini. The flanking half-ridges correspond to the two flanking columns of  $\beta$ -hairpins, which interact with the central column through turn-turn recognition. The ridge period expected from this model is 55 Å: 25.0 Å for each hairpin, 2 Å for the gap at the termini-to-termini interface (a typical distance for hydrogen bonds<sup>[26]</sup>), and 3 Å for the gap at the turn-to-turn interface (a typical distance for van der Waals interactions<sup>[27]</sup>). The panel in the bottom left shows a top view (lower part of panel) and a side view (upper part) of a single hairpin. The hairpin's length is 25 Å and its width is 9.4 Å (see top view), while its height can be from 7 to 10 Å depending on the side chains' conformations (see side view). The green spheres represent the DMBDY fluorophore.

having the D-prolines in the turns rather than in the strands, the model accounts for proline's strong propensity to break  $\beta$ -sheet structure.<sup>[3, 23, 24]</sup> The model is also consistent with the molecular areas determined from the  $\Pi$ -A isotherms. The molecular areas based on the hairpin dimensions and the measured ridge periods are  $9.4 \text{ \AA} \times \frac{1}{2} \times 59 \text{ \AA} = 277 \text{ \AA}^2$  for **1** and  $9.4 \text{ \AA} \times \frac{1}{2} \times 74 \text{ \AA} = 348 \text{ \AA}^2$  for **2**. These are within 18% and 9% of their experimentally determined values ( $230 \text{ \AA}^2$  and  $320 \text{ \AA}^2$ ). Finally, the model accounts for how peptide length can be used to control the ridge period. Because the strands are perpendicular to the ridges, **2** should produce ridge periods  $13.8 \text{ \AA}$  longer than those of **1** since it is four residues longer ( $4 \times 3.45 \text{ \AA}$ ). This is within 8% of the observed difference.

In summary, AFM images obtained using single-wall carbon nanotube tips show that LB monolayers of **1** and **2** are organized into two-dimensional domains of laterally assembled cross- $\beta$  sheets. These sheets appear as ridges in the AFM images. Individual domains extend for hundreds of nanometers in LB monolayers of **1** and tens of nanometers in LB monolayers of **2**. Finally, the size of the ridges can be directly controlled through the peptide length.

### Experimental Section

The preparation of **1** has been described elsewhere.<sup>[13]</sup> Peptide **2** was prepared by the same method and characterized by electrospray ionization mass spectrometry ( $M^- = 2360.7$ , expected: 2360.3). Peptides were spread from solutions in 1:1 DIW:ethanol. Isotherms were measured 30 min after spreading on DIW at room temperature on a Nima 611 LB Trough with a compression rate of  $5 \text{ cm}^2 \text{ min}^{-1}$ . See Supporting Information for details of peptide concentration determination in the spreading solutions and subphase. LB films were deposited using a KSV 5000 LB trough by rapidly compressing monolayers to  $10 \text{ mN m}^{-1}$ , holding for 10 min, then lifting freshly cleaved mica substrates through the surface at  $2 \text{ mm min}^{-1}$ . AFM measurements were made in air using a Digital Instruments Multimode Nanoscope IIIa in Tapping Mode. SWNT tips were prepared as described previously.<sup>[25]</sup>

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## An Unprecedented Mixed-Charged State in a Supramolecular Assembly of Ligand-Based Mixed-Valence Redox Isomers (ET<sup>+</sup>)<sub>3</sub>[Cr<sup>III</sup>-(Cl<sub>4</sub>SQ)<sub>2</sub>(Cl<sub>4</sub>Cat)]-[Cr<sup>III</sup>(Cl<sub>4</sub>SQ)(Cl<sub>4</sub>Cat)<sub>2</sub>]<sup>2-\*</sup>

Ho-Chol Chang and Susumu Kitagawa\*

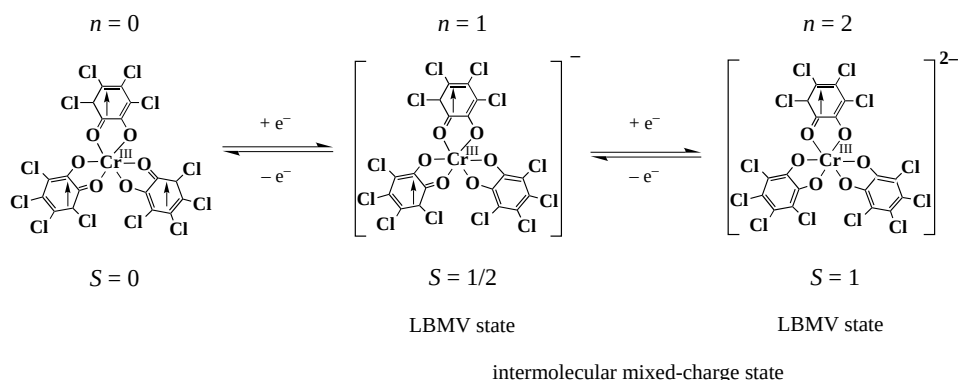
A metal complex containing noninnocent ligands serves as a useful module for synthesizing functional supramolecular assemblies whose physical and/or chemical properties are based on charges and spins. This is exemplified by the family of homoleptic *o*-quinone complexes, which provides unique charged and spin states irrespective of their simple constituent, C<sub>6</sub>O<sub>2</sub>X<sub>4</sub> (X = H or a halogen atom).<sup>[1]</sup> The freedom of their electronic states, for instance, is related to the redox forms of the ligand; *o*-benzoquinone, (BQ), *o*-semiquinonate (SQ), and catecholate (Cat). We have focused our interest on the ligand-based mixed-valence (LBMV) state of the ligands,

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.





Scheme 1.

and have previously prepared charge transfer (CT) compounds of the series of redox isomers  $[\text{Cr}^{\text{III}}(\text{X}_4\text{SQ})_{3-n}(\text{X}_4\text{Cat})_n]^{n-}$  ( $\text{X} = \text{Cl}$  and  $\text{Br}$ ,  $n=0-2$ ) (Scheme 1) by the reaction of tris(tetrahalogeno-*o*-semiquinonato)chromium(III),  $\text{Cr}^{\text{III}}(\text{X}_4\text{SQ})_3$ , with several donor molecules.<sup>[2]</sup> The intramolecular antiferromagnetic nature of the  $\text{Cr}^{\text{III}}-\text{SQ}$  moieties provides  $S=0$ ,  $1/2$ , and  $1$  magnetic ground states for the  $n=0$ ,  $1$ , and  $2$  isomers, respectively, accompanied by their oxidation states (Scheme 1).<sup>[2, 3]</sup>

The intra- and intermolecular freedom with regard to the charge and spin may allow the creation of a novel type of molecular assembly containing new supramolecular synthons,<sup>[4]</sup> such as  $\text{SQ} \cdots \text{SQ}$  magnetic type,  $\text{SQ} \cdots \text{Cat}$  CT type, and cation  $\cdots$  Cat and cation  $\cdots$  SQ interactions, in terms of the oxidation state of the ligands. Herein, we present an unprecedented phase of a molecular assembly from a mixed-charge isomer, which displays unique properties.

The reaction of  $\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_3$  with bis(ethylenedithio)tetrathiafulvalene (ET) yields an insoluble black crystalline product, which has the stoichiometry of  $(\text{ET})_3[\text{Cr}(\text{Cl}_4\text{C}_6\text{O}_2)_3]_2$  (**1**).<sup>[5]</sup> The crystal structure of **1** (Figure 1 a) is composed of a two-dimensional (2D) layer constructed from the mix-stacked ET and chromium complexes. The layer contains three independent  $\pi \cdots \pi$  interactions between the ligands of the chromium complexes and ET units, namely,  $[\text{I} \cdots \text{A}]$ ,  $[\text{I} \cdots \text{C}]$ , and  $[\text{II} \cdots \text{B}]$  (see Figure 1 a). The interplanar spacings and dihedral angles are  $3.513(4)$ ,  $3.598(4)$ , and  $3.435(3)$ , and  $6.7$ ,  $4.7$ , and  $12^\circ$  for  $[\text{I} \cdots \text{A}]$ ,  $[\text{I} \cdots \text{C}]$ , and  $[\text{II} \cdots \text{B}]$ , respectively. Each ET unit is encapsulated by the four ligands of the two chromium complex anions, leading to a ratio of  $\text{ET}:[\text{Cr}]$  of  $3:2$ ; ET unit A is arranged in a face-to-face fashion with ligands I and I' (Figure 1 b), while ligands III and III' lie nearly perpendicular to the ET unit A (Figure 1 c). Similarly, ET unit B (C) is surrounded by ligands II (I) (parallel), II' (I') (parallel), III (II) (perpendicular), and III' (II') (perpendicular).

In addition to the  $\pi \cdots \pi$  interactions, an atomic contact<sup>[7]</sup> between the S(8) and S(8\*) atoms of the adjacent ET unit B results in a one-dimensional (1D) chain structure along the *a* axis (Figure 1 d). The contact renders the layers to be packed closely with an  $\text{S} \cdots \text{S}$  distance of  $3.321(3)$  Å, which is shorter than the sum of the van der Waals radii (3.7 Å).

The oxidation state of the ET molecule was estimated to be  $+1.011$ ,  $+1.324$ , and  $+1.183$  for A, B, and C, respectively, by

using the well-known correlation:  $Q$  (estimated charge) =  $6.347 - 7.463\delta$ , where the parameter  $\delta$  is defined by the four bond lengths of the ET molecule.<sup>[8]</sup> In addition, compound **1** displays an IR band at  $1394 \text{ cm}^{-1}$  and two Raman bands at  $1416$  and  $1450 \text{ cm}^{-1}$  at  $296 \text{ K}$ , which indicates a charge of  $+1$  for the ET molecules.<sup>[9]</sup> Based on this spectroscopic evidence and on the composition of the compound, a

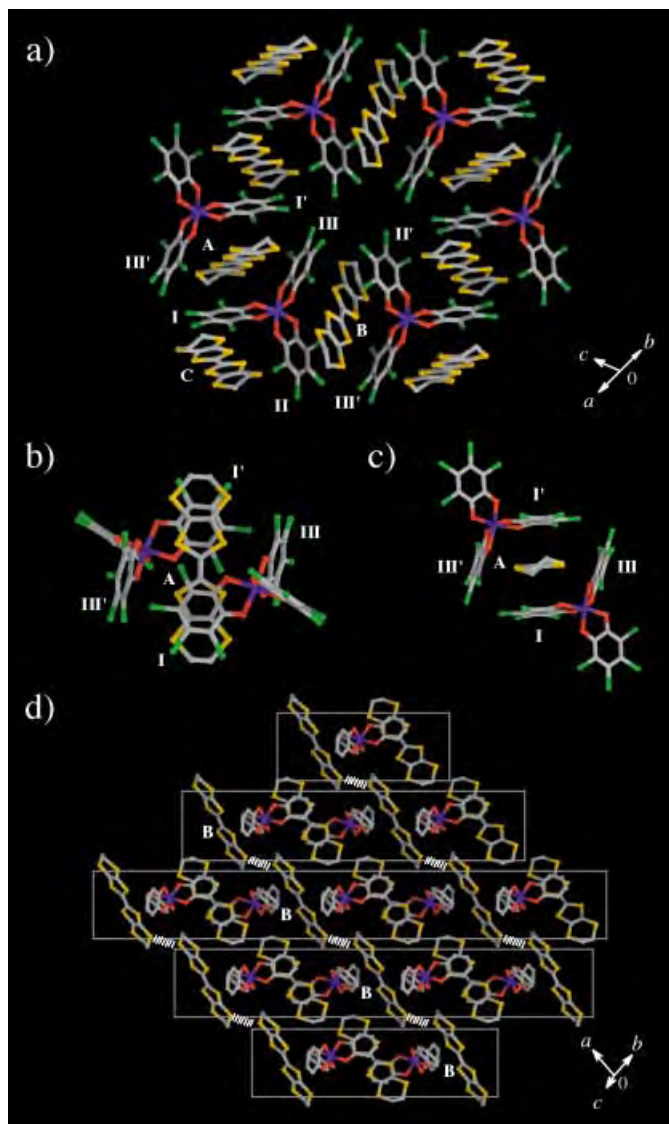


Figure 1. a) Stick representations of 2D layer, b) top, and c) side views of the interactions between ET unit A and ligands I, I', III, and III' (ET units B and C have similar packing structures with the surrounding ligands). d) 3D crystal packing structures of **1**. The dashed lines indicate the intermolecular  $\text{S}(8) \cdots \text{S}(8^*)$  contacts (the chlorine atoms are omitted for clarity). Crystallographically independent ligands and ET units are designated I–III and A–C, respectively. Color code; C: gray, O: red, Cl: green, Cr: blue, S: yellow. Average bond lengths [Å] and angles  $^\circ$ : Cr–O  $1.941(2)$ , C–O  $1.312(4)$ , C–C (chromium complex)  $1.399(5)$ , central C–C (ET unit A)  $1.376(7)$ , central C–C (ET unit B)  $1.401(6)$ , central C–C (ET unit C)  $1.389(7)$ ; O–Cr–O  $82.9(1)^\circ$ .



−3 charge should be distributable over two chromium complexes. As regards the structural parameters for the chromium complexes, only one crystallographically independent anion is found in which the average C–O bond lengths and O–Cr–O angles (Figure 1) are longer than those of  $\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_3$ ,<sup>[10]</sup> indicating the reduction occurs on the ligand moieties.

Figure 2a shows a NIR-IR absorption spectrum of **1** (KBr) compared with those of the  $n=1$  and  $n=2$  isomers. Compound **1** displays absorption maxima at 4170 and 5130  $\text{cm}^{-1}$ . The  $n=1$  and  $n=2$  isomers are well-characterized by the

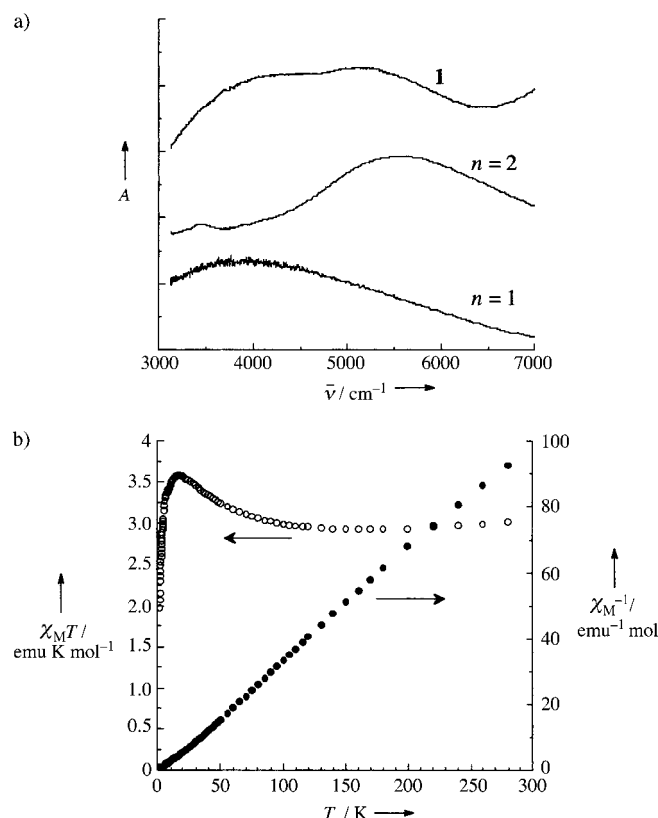


Figure 2. a) NIR-IR absorption spectra of **1** (top) and  $(\text{Co}^{\text{III}}\text{Cp}_2)_n[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_{3-n}(\text{Cl}_4\text{Cat})_n]$  ( $n=1$  (bottom) and  $n=2$  (middle)).<sup>[2]</sup> b) Temperature dependence of  $\chi_M T$  (○) and  $\chi_M^{-1}$  (●) of **1** under the field of 1 T.

intramolecular intervalence CT (IVCT) transition from Cat to SQ at 3920 and 5560  $\text{cm}^{-1}$ , respectively.<sup>[2]</sup> From the comparison of these absorption bands with those of **1**, the bands at 4170 and 5130  $\text{cm}^{-1}$  are assigned to the IVCT transition bands of the  $n=1$  and  $n=2$  isomers in **1**, respectively. Thus, this spectrum is consistent with the coexistence of both *intramolecular* mixed-valence  $[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_2(\text{Cl}_4\text{Cat})]^-$  ( $n=1$ ) and  $[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})(\text{Cl}_4\text{Cat})_2]^{2-}$  ( $n=2$ ) isomers in the crystal of **1**, which exhibits the *intermolecular* mixed-charge state (Scheme 1). Consequently, compound **1** is best formulated as  $(\text{ET}^+)_3[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_2(\text{Cl}_4\text{Cat})]^-[\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})(\text{Cl}_4\text{Cat})_2]^{2-}$ .

A single crystal of compound **1** shows electric conductivity of  $\sigma = 0.0076 \text{ S cm}^{-1}$  at 293 K, and its temperature dependence (77–296 K) reveals that **1** is a semiconductor with an activation energy of 0.14 eV.<sup>[11]</sup> The magnetic properties of

compound **1** are shown in Figure 2b in the form of a  $\chi_M T$  versus  $T$  curve and a  $\chi_M^{-1}$  versus  $T$  curve ( $\chi_M$  value is given per  $(\text{ET})_3[\text{Cr}(\text{Cl}_4\text{C}_6\text{O}_2)_3]_2$  unit). At 300 K, the  $\chi_M T$  value is 3.05  $\text{emu K mol}^{-1}$ , which first decreases very slowly, then gradually increases as the temperature is lowered down to 17 K and reaches a maximum at that temperature with a  $\chi_M T$  value of 3.58  $\text{emu K mol}^{-1}$ . When the temperature is lowered below 17 K, the value of  $\chi_M T$  decreases to 1.98  $\text{emu K mol}^{-1}$  (at 1.9 K). Based on the structural and spectroscopic data, five different magnetic components come from 1) the  $n=1$  and 2) the  $n=2$  isomers with  $S=1/2$  and 1 ground states, respectively,<sup>[2]</sup> and finally 3) three  $\text{ET}^+$  ions with  $S=1/2$  spin. The observed value at 300 K is slightly larger than the theoretical value of 2.50  $\text{emu K mol}^{-1}$  (derived from  $0.375$  ( $n=1$  isomer with  $S=1/2$ ) +  $1.0$  ( $n=2$  isomer with  $S=1$ ) +  $3 \times 0.375$  ( $3 \times \text{ET}^+$  with  $S=1/2$ ) assuming  $g=2.00$ ). The decrease of the value of  $\chi_M T$  in the region of 150–300 K is due to an increase in the population for the ground state of the  $n=1$  and  $n=2$  isomers,<sup>[2]</sup> while the increase of the value of  $\chi_M T$  below 150 K clearly indicates the presence of a dominant ferromagnetic interaction. For the latter, the possible intermolecular interactions occur in 1)  $[\text{ET}]^+ \cdots [\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})(\text{Cl}_4\text{Cat})_2]^{2-}$ , 2)  $[\text{ET}]^+ \cdots [\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_2(\text{Cl}_4\text{Cat})]^-$ , and 3)  $[\text{ET unit B}]^+ \cdots [\text{ET unit B}]^+$ . Although it is not clear which one is responsible for the observed ferromagnetic coupling, the best candidate seems to be 1) and/or 2) because of their stacked structures. While the intramolecular electronic structures and magnetic properties of the transition metal complexes with *o*-quinone ligands have been extensively studied,<sup>[1, 12]</sup> compound **1** first provides a principle for designing molecular assemblies in a ternary system by using redox-active transition metal complexes. The results obtained in this study indicate that the flexibility and diversity of charged and spin states of the *o*-quinone complexes open up a new dimension to the chemistry of molecular assemblies.

## Experimental Section

ET was purchased from Tokyo Kasei Kogyo Co., Ltd.  $\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_3 \cdot 4 \text{ C}_6\text{H}_6$  was prepared by the procedure described previously.<sup>[2a]</sup>

**1**: Single crystals of **1** were grown from a layered solution of a solution of  $\text{Cr}^{\text{III}}(\text{Cl}_4\text{SQ})_3 \cdot 4 \text{ C}_6\text{H}_6$  (0.227 mm) in  $\text{CH}_2\text{Cl}_2$  and a solution of ET (0.481 mm) in  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$  (2:1). Black plate crystals were obtained after a week. Elemental analysis (%) calcd for  $\text{C}_{66}\text{H}_{24}\text{Cl}_{24}\text{Cr}_2\text{O}_{12}\text{S}_{24}$ : C 29.0, H 0.89; found: C 29.04, H 0.73; IR peaks (KBr):  $\tilde{\nu} = 1397\text{s}, 1315\text{w}, 1284\text{m}, 1111\text{s}, 1024\text{m}, 977\text{s}, 925\text{vw}, 894\text{w}, 882\text{w}, 810\text{w}, 792\text{s}, 737\text{w}, 691\text{w}, 670\text{vw}, 552\text{w}, 478\text{w}, 450\text{m cm}^{-1}$ .

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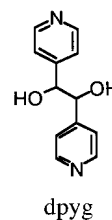
- [5] Crystal data for **1**: Crystal dimensions  $0.60 \times 0.50 \times 0.50 \text{ mm}^3$ ,  $\text{C}_{66}\text{H}_{24}\text{Cl}_{24}\text{Cr}_2\text{O}_{12}\text{S}_{24}$ ,  $M_r = 2733.21$ , triclinic,  $P\bar{1}$ ,  $a = 12.4074(9)$ ,  $b = 14.554(1)$ ,  $c = 15.270(2) \text{ \AA}$ ,  $\alpha = 117.193(4)$ ,  $\beta = 97.7640(9)$ ,  $\gamma = 96.0637(8)^\circ$ ,  $V = 2386.0(3) \text{ \AA}^3$ ,  $Z = 1$ ,  $\rho_{\text{calc}} = 1.902 \text{ g cm}^{-3}$ ,  $2\theta_{\text{max}} = 55.1^\circ$ ,  $\text{MoK}\alpha$ ,  $\lambda = 0.71069 \text{ \AA}$ ,  $\omega$  scan, 296 K, 10915 independent reflections, number of reflections included in the refinement = 7092 ( $I > 4.0\sigma(I_0)$ ), and  $R(wR) = 0.037(0.048)$ . The intensity data were collected on a Rigaku mercury CCD area detector. Empirical absorption correction was performed by using the program REQABA.<sup>[6a]</sup> The structures were solved by direct methods (SIR92).<sup>[6b]</sup> All the calculations were performed by using the teXsan crystallographic software package from the Molecular Structure Corporation.<sup>[6c]</sup> 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-165306 (**1**). 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 Pillared-Layer Coordination Polymer Network Displaying Hysteretic Sorption: $[\text{Cu}_2(\text{pzdc})_2(\text{dpyg})]_n$ (pzdc = Pyrazine-2,3-dicarboxylate; dpyg = 1,2-Di(4-pyridyl)-glycol)\*\*

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Recently developed porous coordination polymers have added a new dimension to materials-directed coordination chemistry; applications of these compounds range from gas storage and ion exchange to heterogeneous catalysis.<sup>[1–4]</sup> The key to this success is the establishment of permanent porosity even in the absence of guest molecules as well as inorganic zeolites, to afford the desired robust three-dimensional (3D) frameworks of metal ions and organic ligands. The next challenge is to develop a dynamic porous compound, a so-called third-generation compound,<sup>[5]</sup> which responds to a specific guest molecule and changes its microcavities into those well-suited for the shape and/or affinity of the guest molecule. Metal complex based compounds in this category are emerging<sup>[6–10]</sup> but still few. Herein, we have focused on developing the rational design and synthesis of this kind of framework. We have employed a pillared-layer motif because simple modification of the pillar module can control not only the channel size and shape but also the chemical functionality. The prototype structure was obtained by using  $\text{Cu}^{2+}$ ,  $\text{Na}_2\text{pzdc}$  (pzdc = pyrazine-2,3-dicarboxylate), and a series of pillar ligands of pyridine derivatives.<sup>[11]</sup> We designed the new pillared-layer type coordination polymer with 1,2-dipyridylglycol (dpyg) as a flexible and functional pillar, and examined guest ( $\text{CH}_4$ , MeOH, and  $\text{H}_2\text{O}$ ) inclusion properties.

$[[[\text{Cu}_2(\text{pzdc})_2(\text{dpyg})] \cdot 8\text{H}_2\text{O}]_n]$  (**1**) was synthesized by the reaction of  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  with  $\text{Na}_2\text{pzdc}$  and dpyg in  $\text{H}_2\text{O}/\text{EtOH}$  media. The molecular structure of **1** was determined by X-ray crystallography, and Figure 1 shows the structure around the  $\text{Cu}^{\text{II}}$  centers. Each  $\text{Cu}^{\text{II}}$  atom is five-coordinate, residing in a distorted trigonal-bipyramidal environment, surrounded by three O atoms from three pzdc ligands, and two N atoms from a dpyg and a pzdc ligand. The  $\text{Cu}_2(\mu\text{-O})_2$  units are linked by the pzdc ligands to give a neutral two-dimensional layer in the  $bc$  plane (Figure 2a). The dpyg



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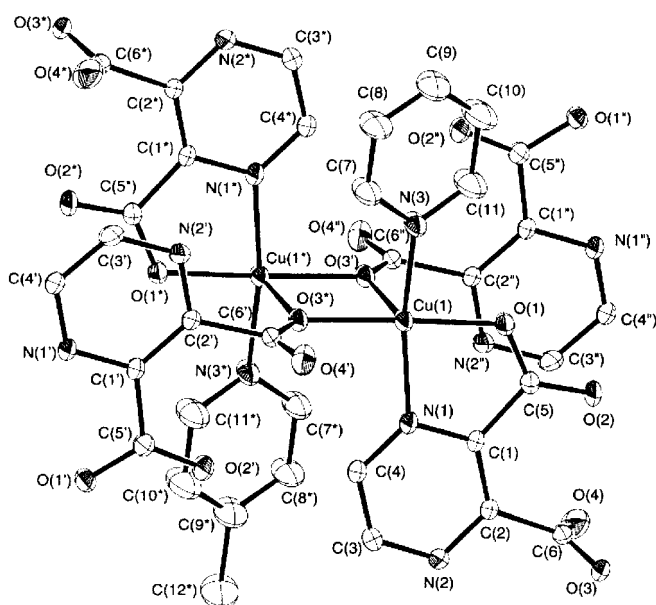


Figure 1. Molecular structure of the dicopper sites of **1** (ORTEP drawing with 30% probabilities). Hydrogen atoms and OH groups are omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)–O(1) 1.928(4), Cu(1)–O(3') 1.973(3), Cu(1)–O(3\*) 2.494(4), Cu(1)–N(1) 2.022(4), Cu(1)–N(3) 2.003(4); O(1)–Cu(1)–O(3') 172.3(2), O(1)–Cu(1)–O(3\*) 96.1(2), O(1)–Cu(1)–N(1) 81.8(2), O(1)–Cu(1)–N(3) 90.6(2), O(3')–Cu(1)–O(3\*) 77.5(1), O(3')–Cu(1)–N(1) 94.3(2), O(3')–Cu(1)–N(3) 94.1(2), O(3\*)–Cu(1)–N(1) 94.6(2), O(3\*)–Cu(1)–N(3) 94.0(2), N(1)–Cu(1)–N(3) 169.0(2).

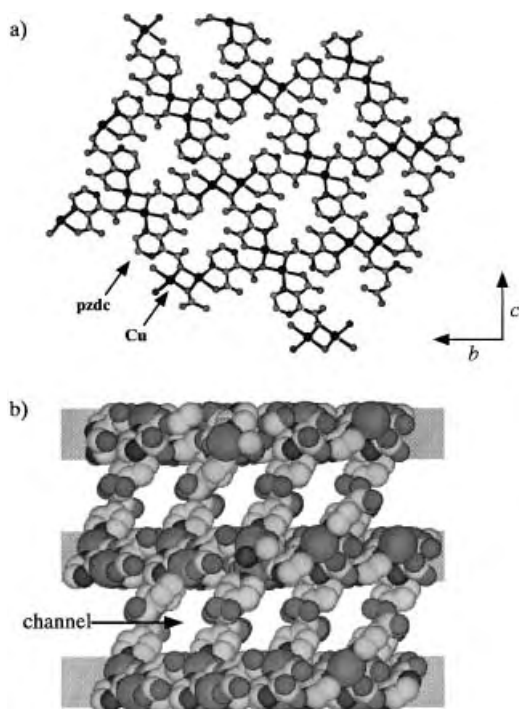


Figure 2. View of the two-dimensional sheet (a) and channel structure (b) of **1**. Solvent water and hydrogen atoms are omitted for clarity.

ligand acts as a pillar;  $\text{Cu}_2(\mu\text{-O})_2$  units in the adjacent layers are linked to form a three-dimensional pillared-layer structure (Figure 2b). The OH groups are disordered because of the racemic nature of the dpyg ligands. The framework provides interlayer spaces (ca. 33% porosity), resulting in

microchannels with a cross section of  $4 \times 6 \text{ Å}$  in size.<sup>[12]</sup> Interestingly, all the OH groups of the dpyg ligands are not utilized for the coordination framework but for coordinating guest molecules in the channel. As a result, **1** includes water molecules, which are hydrogen-bonded to the OH groups as well as to the nearest neighbor water molecules.

The thermogravimetric profile of **1** shows that the on-set of the release of the crystalline water molecules occurs at  $60^\circ\text{C}$ , and that the structure decomposition occurs at  $220^\circ\text{C}$ . No weight change was observed between  $140^\circ\text{C}$  and  $220^\circ\text{C}$ , where a guest-free phase (anhydrous **1**, therefore apohost **2**), is maintained. Figure 3 shows the X-ray powder diffraction (XRPD) patterns of **1** and **2**. The XRPD pattern of **2** has sharp diffraction peaks, indicating that the porous framework is

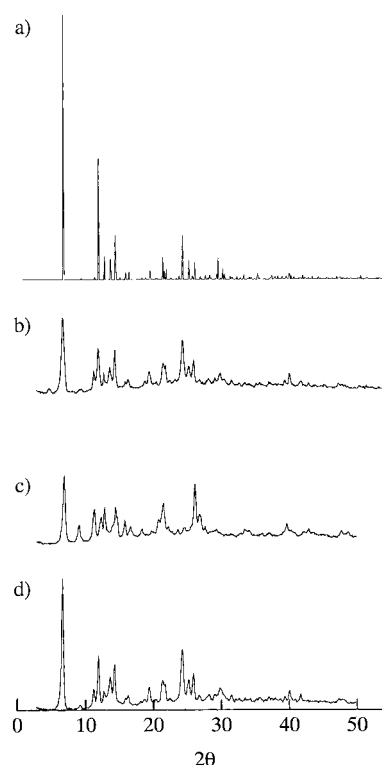


Figure 3. a) Simulated XRPD pattern upon removal of the water molecules from the single crystal. Observed XRPD patterns of as-synthesized sample **1** (b), anhydrous sample **2** (dried at  $110^\circ\text{C}$  under reduced pressure for 5 h) (c), and MeOH immersed sample after drying (d)

maintained even without guest molecules. The initial framework of **1** undergoes a slight change to become that of **2**; for instance, a peak (100) at  $6.80^\circ$  for **1** moves to  $7.10^\circ$  for **2**, exhibiting a slight decrease in the layer distance. In practice, the original framework is completely reformed when immersed in  $\text{H}_2\text{O}$  or MeOH. It should be emphasized that this transformation of crystal **2** to crystal **1** occurs even when exposed to  $\text{H}_2\text{O}$  or MeOH vapor. Consequently, this structural change can take place reversibly in the process of evacuation under reduced pressure/exposure to the guest vapors.

We measured the adsorption isotherms for  $\text{CH}_4$ ,  $\text{H}_2\text{O}$ , and MeOH to examine the porous properties. The adsorption isotherm of  $\text{CH}_4$  for **2** at 298 K reveals no uptake into the

micropores at all, indicating that the channel of **2** is not large enough to incorporate CH<sub>4</sub> molecules (3.8 × 3.8 Å). On the other hand, MeOH, irrespective of its similar size to that of CH<sub>4</sub>, can be adsorbed, as well-illustrated in Figure 4. The

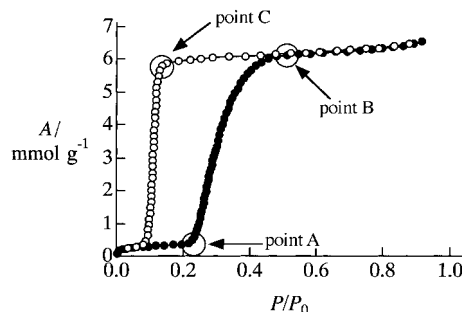


Figure 4. Methanol adsorption (filled circles) and desorption (open circles) isotherms at 298 K. A = absolute adsorption.

isotherm shows a sudden rise at point A (relative pressure,  $P/P_0$ , is 0.23) and attains a saturated level (ca. 6.2 mmol g<sup>-1</sup>) at point B ( $P/P_0 = 0.5$ ). On the other hand, the desorption isotherm does not trace the adsorption one any more, instead, showing an abrupt drop at point C ( $P/P_0 = 0.1$ ). This hysteretic profile between the adsorption and desorption isotherms was reproducible many times. This sharp adsorption jump/desorption drop with the hysteresis indicates the occurrence of a framework transformation in the crystal state, which should permit guest inclusion.<sup>[13, 14]</sup> The BET surface area calculated from the adsorption isotherm in the region between zero and point A is 37 m<sup>2</sup> g<sup>-1</sup>. Thus only surface adsorption for MeOH as well as CH<sub>4</sub> occurs before the point A. Then, after point A, MeOH molecules can diffuse into the channels, whereas CH<sub>4</sub> molecules do not. This is chiefly associated with the hydrogen bonding interaction between the MeOH molecules and the OH groups of the dpyg ligands; the attractive force should be strong enough to transform the channel structure to allow the incorporation of the guest molecules. The structural distortion is confirmed by the XRPD measurements shown in Figure 3. A similar adsorption isotherm with a hysteresis profile is observed in the case of H<sub>2</sub>O vapor. The estimated micropore volume from the MeOH adsorption isotherm is 0.25 mL g<sup>-1</sup>,<sup>[15]</sup> indicating that MeOH vapor is included in the porous network.

The use of a pillared layer motif for the rational synthesis of a novel coordination polymer that displays a hysteretic isotherm, which is based on the response of the flexible and dynamic framework to specific guest molecules, opens up a new field in porous coordination materials.

### Experimental Section

**1:** Cu(ClO<sub>4</sub>)<sub>2</sub> · 6H<sub>2</sub>O (0.37 g) in H<sub>2</sub>O/EtOH (1:1; 100 mL) was slowly added to a solution of dpyg (0.21 g) and Na<sub>2</sub>pzdc (0.21 g) in H<sub>2</sub>O/EtOH (1:1; 100 mL). The blue microcrystals obtained were collected by filtration, and dried under reduced pressure for 5 h. Finally, apohost **2** was obtained. Yield 0.37 g (55 %). Elemental analysis calcd for C<sub>24</sub>H<sub>16</sub>Cu<sub>2</sub>N<sub>6</sub>O<sub>10</sub> (%): C 42.67, H 2.39, N 12.44; found: C 41.22, H 2.31, N 12.48.

X-ray structure determination of **1**: Measurements were recorded on a Rigaku mercury CCD diffractometer with graphite-monochromated MoK $\alpha$  radiation. All calculations were performed by using the teXsan crystallo-

graphic software package from the Molecular Structure Corporation. Crystal data: C<sub>24</sub>H<sub>16</sub>Cu<sub>2</sub>N<sub>6</sub>O<sub>10</sub>,  $M_r = 799.48$ , monoclinic, space group  $P2_1/c$  (no. 14),  $a = 13.1990(9)$ ,  $b = 13.631(2)$ ,  $c = 9.650(3)$  Å,  $\beta = 104.556(1)^\circ$ ,  $V = 1680.5(4)$  Å<sup>3</sup>,  $T = 298$  K,  $Z = 2$ ,  $\rho_{\text{calcd}} = 1.580$  g cm<sup>-3</sup>,  $\lambda(\text{MoK}\alpha) = 0.71069$  Å,  $F(000) = 800$ ,  $\mu(\text{MoK}\alpha) = 13.4$  cm<sup>-1</sup>,  $2\theta_{\text{max}} = 55.2^\circ$ , 3719 reflections measured, 2638 observed ( $I > 2.00\sigma(I)$ ), 215 parameters;  $R = 0.071$ ,  $R_w = 0.095$ . 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-168595. 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).

Gas adsorption measurements: The sorption isotherm measurements for MeOH and H<sub>2</sub>O were performed at 298 K by using an automatic volumetric adsorption apparatus (BELSORP18; BEL inc). A known weight (200–300 mg) of the as-synthesized sample was placed in the quartz tube, then, prior to measurements, the sample was dried under high vacuum at 373 K for 5 h to remove the solvated water molecules. The adsorbate was placed into the sample tube, then the change of the pressure was monitored and the degree of adsorption was determined by the decrease of the pressure at the equilibrium state.

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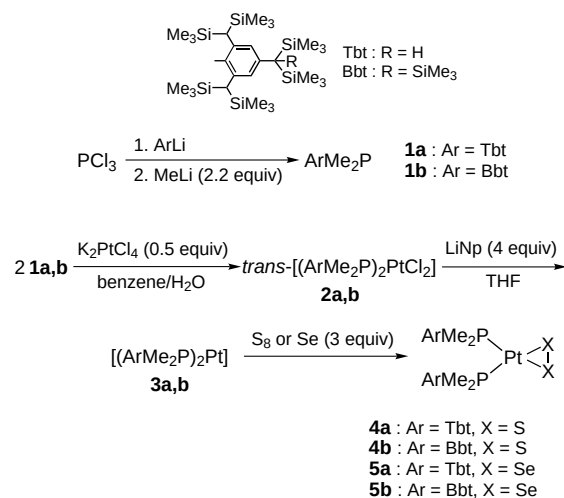
# The First Disulfur and Diselenium Complexes of Platinum: Syntheses and Crystal Structures\*\*

Kazuto Nagata, Nobuhiro Takeda, and Norihiro Tokitoh\*

Various kinds of transition metal compounds containing a polychalcogenido ligand have been synthesized and characterized.<sup>[1]</sup> In particular, the chemistry of complexes with diatomic chalcogen ligands has attracted much attention because of their unique structure,<sup>[2]</sup> biological interest,<sup>[3]</sup> potential for hydrogen-transfer catalysis,<sup>[2]</sup> and synthetic utility as a precursor of new metal cluster complexes.<sup>[4]</sup> However, since sulfur and selenium ligands have a strong propensity for bridging metal atoms, it is often difficult to prepare their mononuclear diatomic complexes.<sup>[2, 5]</sup> As for mononuclear platinum polychalcogenido compounds, most of the complexes obtained so far are limited to PtE<sub>5</sub> or PtE<sub>4</sub> (E = S, Se) ring systems, for example, [(NH<sub>4</sub>)<sub>2</sub>Pt(S<sub>3</sub>)<sub>3</sub>],<sup>[6]</sup> [(PPh<sub>3</sub>)<sub>2</sub>PtS<sub>4</sub>],<sup>[7]</sup> and [(dppe)PtSe<sub>4</sub>] (dppe = 1,2-bis(diphenylphosphino)ethane).<sup>[8]</sup> To our knowledge, the disulfur and diselenium complexes of platinum remain unknown, although the dioxygen analogues, for example, [(Ph<sub>3</sub>P)<sub>2</sub>PtO<sub>2</sub>],<sup>[9]</sup> have been extensively studied.<sup>[10]</sup> Lorenz et al. have reported that the reaction of [(PPh<sub>3</sub>)<sub>2</sub>Pt(C<sub>2</sub>H<sub>4</sub>)] with thiirane *S*-oxide afforded the corresponding disulfur dioxide complex [(PPh<sub>3</sub>)<sub>2</sub>PtS<sub>2</sub>O<sub>2</sub>], which was characterized by elemental analysis and mass spectrometry, IR, and <sup>31</sup>P NMR spectroscopy.<sup>[11]</sup> However, synthesis of a disulfur complex [(PPh<sub>3</sub>)<sub>2</sub>PtS<sub>2</sub>] by the analogous reaction with thiirane was not successful.

Meanwhile, we have reported the synthesis of cyclic polychalcogenides containing a heavier main group element [Tbt(R)ME<sub>4</sub>] (M = Si, Ge, Sn, or Pb; E = S or Se; Tbt = 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl),<sup>[12]</sup> [Tbt(R)MSe<sub>2</sub>] (M = Si or Sn),<sup>[12a,b, 13]</sup> and [TbtSbS<sub>n</sub>] (*n* = 5, 7)<sup>[14]</sup> by taking advantage of the extremely bulky substituent, the Tbt group. On the basis of these results, we envisioned that the introduction of this bulky substituent onto a phosphorus atom which should coordinate to platinum centers might be useful for the synthesis of novel classes of platinum polychalcogenido complexes. Here, we report the synthesis and characterization of the first mononuclear disulfur and diselenium complexes of platinum by utilizing extremely bulky phosphane ligands bearing a Tbt or 2,6-bis[bis(trimethylsilyl)methyl]-4-[tris(trimethylsilyl)methyl]phenyl (Bbt) group.

Bulky phosphane ligands **1** were readily prepared by the treatment of a THF solution of ArLi (Ar = Tbt, Bbt) with an equimolar amount of phosphorous trichloride followed by the addition of a solution of MeLi (2.2 equiv) in diethyl ether (Scheme 1).<sup>[15]</sup> Reaction of **1a,b** with K<sub>2</sub>PtCl<sub>4</sub> in benzene/H<sub>2</sub>O at room temperature for 7 days afforded gray precipitates of



Scheme 1. Syntheses of disulfur and diselenium complexes of platinum, **4** and **5**. See text for full details.

*trans*-[(ArMe<sub>2</sub>P)<sub>2</sub>PtCl<sub>2</sub>] (**2a,b**), which were hardly soluble in common organic solvents except for chloroform. When platinum dichlorides **2a,b** were reduced by an excess of lithium naphthalenide (LiNp) in THF and the resulting platinum(0) species [(ArMe<sub>2</sub>P)<sub>2</sub>Pt] (**3a,b**)<sup>[16]</sup> were successively treated with elemental sulfur (3 equiv as S), the first platinum disulfur complexes [(ArMe<sub>2</sub>P)<sub>2</sub>PtS<sub>2</sub>] (**4a,b**) were obtained as major products together with ArMe<sub>2</sub>P = S and a trace amount of unidentified platinum polysulfido complexes, which could be converted into **4a,b** by further treatment with triphenylphosphane. The structures of **4a,b** were identified by mass spectrometry, elemental analysis, and multinuclear NMR spectroscopy, and the molecular structure of **4b** was determined by X-ray crystallographic analysis (Figure 1 and Table 1).<sup>[17]</sup>

The formation of **4a,b** having a novel PtS<sub>2</sub> ring system is in sharp contrast to the reaction of [(Ph<sub>3</sub>P)<sub>4</sub>Pt] and [(dppe)<sub>2</sub>Pt]

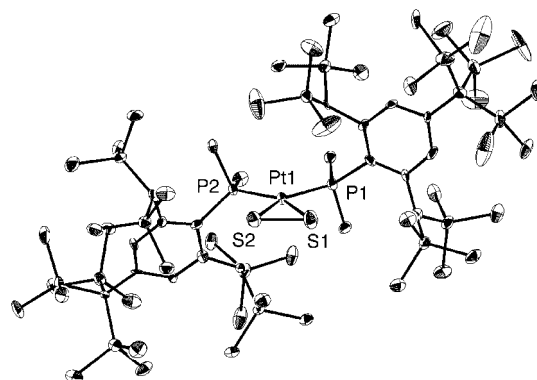


Figure 1. ORTEP drawing of **4b** with thermal ellipsoids set at 50% probability.

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Table 1. Selected bond lengths [Å] and angles [°] for **4b** and **5b**.

| 4b           |           | 5b          |            |
|--------------|-----------|-------------|------------|
| Bond lengths |           |             |            |
| Pt1-S1       | 2.348(3)  | Pt1-Se1     | 2.4491(10) |
| Pt1-S2       | 2.337(3)  | Pt1-Se2     | 2.4658(10) |
| S1-S2        | 2.077(3)  | Se1-Se2     | 2.3363(11) |
| Pt1-P1       | 2.271(2)  | Pt1-P1      | 2.271(2)   |
| Pt1-P2       | 2.265(3)  | Pt1-P2      | 2.261(2)   |
| Bond angles  |           |             |            |
| S1-Pt1-S2    | 52.63(9)  | Se1-Pt1-Se2 | 56.76(3)   |
| Pt1-S1-S2    | 63.41(11) | Pt1-Se1-Se2 | 61.98(3)   |
| Pt1-S2-S1    | 63.96(11) | Pt1-Se2-Se1 | 61.26(3)   |
| P1-Pt1-S1    | 102.07(9) | P1-Pt1-Se1  | 95.44(6)   |
| P2-Pt1-S2    | 98.47(9)  | P2-Pt1-Se2  | 99.94(6)   |
| P1-Pt1-P2    | 106.87(8) | P1-Pt1-P2   | 107.85(7)  |

with elemental sulfur giving the corresponding tetrasulfido complexes,  $[(\text{Ph}_3\text{P})_2\text{PtS}_4]$  and  $[(\text{dppe})\text{PtS}_4]$ , respectively.<sup>[7a]</sup> The diselenium analogues  $[(\text{ArMe}_2\text{P})_2\text{PtSe}_2]$  (**5a,b**), the first platinum diselenium complexes, were also obtained when elemental selenium was used instead of elemental sulfur as shown in Scheme 1. In contrast to the synthesis of **4**, complexes **5** were produced without any other platinum products, but the differences in reactivity of **3** toward sulfur and selenium are unclear at present. The structure of **5b** was also determined by X-ray crystallographic analysis (Figure 2, Table 1).<sup>[17]</sup>

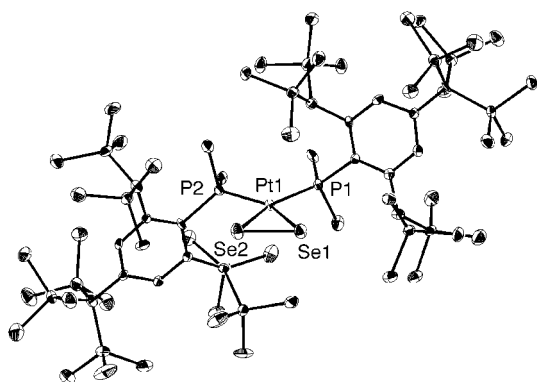


Figure 2. ORTEP drawing of **5b** with thermal ellipsoids set at 50% probability.

Crystallographic analysis showed that **4b** and **5b** are isomorphous and their geometries are very similar. In both cases, the platinum atoms have approximately square-planar geometries and the two Bbt groups are situated in *trans* position with regard to the  $\text{P}_2\text{PtE}_2$  (E = S, Se) plane to decrease the steric congestion. The E1–E2 bond lengths and the E1–Pt1–E2 bond angles of the  $\text{PtE}_2$  (E = S, Se) rings are similar to those of other  $\text{ME}_2$  complexes, for example,  $[\text{IrS}_2(\text{dppe})_2]^+$  2.066(6) Å, 50.8(2)°,<sup>[18]</sup>  $[\text{Ru}_2(\text{CO})_2(\mu\text{-CO})(\mu\text{-S})(\text{S}_2)(\mu\text{-dppm})_2]$  2.13(1) Å, 51.8(3)°,<sup>[19]</sup>  $[(\text{TpTP})\text{TiS}_2]$  2.042(3) Å, 52.79(9)° (TpTP = tetra-*p*-tolylporphyrin),<sup>[20]</sup>  $[\text{OsSe}_2(\text{CO})_2(\text{PPh}_3)_2]$  2.321(1) Å, 54.23(2)°,<sup>[21]</sup> and  $[\text{IrSe}_2(\text{dppe})_2]^+$  2.312(3) Å, 54.3(1)°.<sup>[22]</sup> The Pt–E (E = S, Se) and Pt–P bond lengths are close to those for platinum tetrachalcogenido complexes (2.35 (av.), 2.45 (av.), and 2.26 (av.) Å for Pt–S, Pt–Se, and Pt–P, respectively).<sup>[7b, 8, 23]</sup> The average of the two

Pt–Se bond lengths in **5b** is 0.12 Å longer than the average Pt–S bond length in **4b**, and the Se–Se bond of **5b** is 0.26 Å longer than the S–S bond of **4b**. These differences in the bond lengths correlate well with the approximately 0.13 Å larger covalent radius of selenium than that of sulfur.<sup>[24]</sup> It is noteworthy that the P1–Pt1–P2 bond angles are somewhat larger than those for other related platinum polychalcogenido complexes, for example  $[(\text{dppe})\text{PtS}_4]$  86.8(1)°,<sup>[23]</sup>  $[(\text{Ph}_3\text{P})_2\text{PtS}_4]$  99.3(2)°,<sup>[7b]</sup>  $[(\text{Ph}_3\text{P})_2\text{Pt}(\text{S}_3\text{O})]$  98.47(8)°,<sup>[25]</sup>  $[\text{Pt}_2(\mu\text{-S})_2(\text{dppy})_4]$  102.98(6)° (dppy = 2-diphenylphosphinopyridine),<sup>[26]</sup>  $[(\text{dppe})\text{PtSe}_4]$  86.31(20)°,<sup>[8a]</sup>  $[\text{Pt}_2(\mu\text{-Se})_2(\text{PPh}_3)_4]$  99.6(1)°,<sup>[27]</sup> and an analogous dioxygen complex,  $[(\text{Ph}_3\text{P})_2\text{PtO}_2]$  100–101°,<sup>[9]</sup> which reflects the severe steric repulsion between two Bbt groups. We assume that these larger P1–Pt1–P2 angles of **4b** and **5b** contribute to the stabilization of the three-membered  $\text{PtE}_2$  ring systems.<sup>[28]</sup>

The  $^{195}\text{Pt}$  NMR signals of **4b** and **5b** were observed at  $\delta = -4983$  ( $^1J_{\text{Pt,P}} = 3909$  Hz) and  $\delta = -5030$  ( $^1J_{\text{Pt,P}} = 3865$  Hz,  $^1J_{\text{Pt,Se}} = 262$  Hz), respectively. In the  $^{77}\text{Se}$  NMR spectrum of **5b**, only one broad signal was observed at  $\delta = 582$  (see Supporting Information), although the satellite peaks arising from the  $^{77}\text{Se}$ – $^{195}\text{Pt}$  couplings could not be recognized probably because of broadening of the peak. This  $^{77}\text{Se}$  resonance is slightly upfield relative to those for  $^{77}\text{Se}$  atoms bound to the platinum in  $\text{PtSe}_4$  rings,  $[(\text{dppe})\text{PtSe}_4]$   $\delta = 640$ <sup>[8a]</sup> and  $[\text{Pt}(\text{Se}_4)_3^{2-}]$   $\delta = 680$ .<sup>[29]</sup>

Compounds **4** and **5** are both air-stable in the solid state, while they decomposed to the corresponding phosphane chalcogenides and metallic platinum on standing in solution at room temperature for several days.

In conclusion, we successfully prepared the first disulfur and diselenium complexes of platinum **4** and **5** by the reaction of platinum(0) complexes coordinated by monodentate bulky phosphane ligands bearing a Tbt or Bbt group with elemental sulfur and selenium, respectively, and their molecular structures were determined.

## Experimental Section

**4b**: A THF suspension (3 mL) of *trans*- $[(\text{BbtMe}_2\text{P})_2\text{PtCl}_2]$  (**2b**; 123 mg, 0.075 mmol) was treated with a THF solution of lithium naphthalenide (0.82 M, 0.37 mL, 4 equiv) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 1 h while being warmed to room temperature. After stirring for 1 h at room temperature, the solution of  $[(\text{BbtMe}_2\text{P})_2\text{Pt}]$  (**3b**) thus obtained was cooled to  $-78^\circ\text{C}$  and treated with  $\text{S}_8$  (7.2 mg, 0.028 mmol, 3 equiv based on **3b**). The reaction mixture was stirred for 4 h while being warmed to room temperature. After removal of the solvent, chloroform was added to the residue and the mixture was filtered through Celite. The filtrate was evaporated, and the crude product was dissolved in chloroform (3 mL). The solution was treated with triphenylphosphane (39 mg, 0.15 mmol) at  $50^\circ\text{C}$  for 1.5 h, and the solvent was evaporated. The residue was purified by preparative gel permeation liquid chromatography (eluting with  $\text{CHCl}_3$ ) to afford **4b** as a pure pale purple crystalline solid (86 mg, 71%) along with  $\text{BbtMe}_2\text{P}=\text{S}$  (11 mg, 10%); **4b**: m.p. 162.3–163.5  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ )  $\delta = 0.16$  (s, 72H), 0.21 (s, 54H), 2.19 (br m, 12H), 3.32 (s, 4H), 6.65 (s, 4H);  $^{31}\text{P}$  NMR (120 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ , 85%  $\text{H}_3\text{PO}_4$ )  $\delta = -32.2$  ( $^1J_{\text{P,Pt}} = 3909$  Hz);  $^{195}\text{Pt}$  NMR (64 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ,  $\text{Na}_2\text{PtCl}_6$ )  $\delta = -4983$  (d,  $^1J_{\text{P,Pt}} = 3909$  Hz); FAB MS: 1628 [ $M^+$ ]; elemental analysis calcd (%) for  $\text{C}_{64}\text{H}_{146}\text{P}_2\text{PtS}_2\text{Si}_{14}$ : C 47.15, H 9.03; found: C 47.09, H 9.28.

**5b**: Using the same procedure as that for **4b** without the treatment of the crude products with triphenylphosphane, **5b** was obtained as a green crystalline solid (60 mg, 70%) from **2b** (82 mg, 0.050 mmol) and elemental selenium (12 mg, 0.150 mmol); **5b**: m.p. 170.6–171.8  $^\circ\text{C}$ ;  $^1\text{H}$  NMR

(300 MHz, CDCl<sub>3</sub>, 25 °C)  $\delta$  = 0.17 (s, 72 H), 0.22 (s, 54 H), 2.23 (br m, 12 H), 3.33 (s, 4 H), 6.64 (s, 4 H); <sup>31</sup>P NMR (120 MHz, CDCl<sub>3</sub>, 25 °C, 85 % H<sub>3</sub>PO<sub>4</sub>)  $\delta$  = -44.1 (<sup>1</sup>J<sub>PPt</sub> = 3865 Hz); <sup>77</sup>Se NMR (57 MHz, CDCl<sub>3</sub>, 25 °C)  $\delta$  = 582; <sup>195</sup>Pt NMR (64 MHz, CDCl<sub>3</sub>, 25 °C, Na<sub>2</sub>PtCl<sub>6</sub>)  $\delta$  = -5030 (dd, <sup>1</sup>J<sub>Pt,P</sub> = 3865 Hz, <sup>1</sup>J<sub>Pt,Se</sub> = 262 Hz); FAB MS: 1723 [M<sup>+</sup>]; elemental analysis calcd (%) for C<sub>64</sub>H<sub>146</sub>P<sub>2</sub>PtSe<sub>2</sub>Si<sub>14</sub>: C 44.59, H 8.54; found: C 44.32, H 8.59.

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- [15] Since phosphanes **1** were very air-sensitive in solution, **1** could not be obtained in a pure state because of the contamination with trace amounts of oxidized ArMe<sub>2</sub>P=O during the course of workup and purification. However, the structures of **1** were identified by NMR spectroscopy and high resolution mass spectrometry (HRMS calcd for **1b**: C<sub>62</sub>H<sub>73</sub>PSi<sub>7</sub>: 684.3835; found 684.3837).
- [16] The intermediates **3a,b** could be identified by <sup>31</sup>P NMR spectroscopy (120 MHz, C<sub>6</sub>D<sub>6</sub>, 25 °C, relative to 85 % H<sub>3</sub>PO<sub>4</sub>) **3a**:  $\delta_P$  = 0.9, <sup>1</sup>J<sub>PPt</sub> = 3974 Hz, **3b**:  $\delta_P$  = 3.7, <sup>1</sup>J<sub>PPt</sub> = 3869 Hz. These values are in the range

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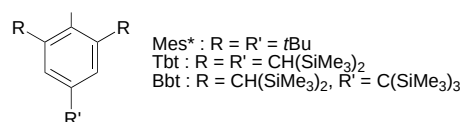
- [17] Crystallographic data for **4b** and **5b**. **4b**: C<sub>64</sub>H<sub>146</sub>P<sub>2</sub>PtSe<sub>2</sub>Si<sub>14</sub>, *M* = 1630.22, monoclinic, space group *Cc* (no. 9), *a* = 40.121(8), *b* = 9.130(3), *c* = 23.740(6) Å,  $\beta$  = 91.2201(19)°, *V* = 8694(4) Å<sup>3</sup>, *Z* = 4,  $\rho_{\text{calcd}}$  = 1.245 g cm<sup>-3</sup>,  $\mu$  = 19.3 cm<sup>-1</sup>, *R*<sub>1</sub> (*wR*<sub>2</sub>) = 0.062 (0.146), *T* = 93(2) K, *GOF* = 1.00. **5b**: C<sub>64</sub>H<sub>146</sub>P<sub>2</sub>PtSe<sub>2</sub>Si<sub>14</sub>, *M* = 1724.02, monoclinic, space group *Cc* (no. 9), *a* = 40.213(2), *b* = 9.1551(15), *c* = 23.860(2) Å,  $\beta$  = 89.0303(7)°, *V* = 8782.8(17) Å<sup>3</sup>, *Z* = 4,  $\rho_{\text{calcd}}$  = 1.304 g cm<sup>-3</sup>,  $\mu$  = 26.9 cm<sup>-1</sup>, *R*<sub>1</sub> (*wR*<sub>2</sub>) = 0.047 (0.127), *T* = 93(2) K, *GOF* = 1.08. The intensity data were collected on a Rigaku Mercury CCD diffractometer with graphite-monochromated MoK $\alpha$  radiation ( $\lambda$  = 0.71070 Å). The structures were solved by direct methods with SIR-97. The three methyl carbon atoms of the one trimethylsilyl group on the Bbt group are disordered in **4b**. In Figure 1, the minor part of the disordered carbon atoms is omitted for clarity. The P<sub>2</sub>PtSe<sub>2</sub> plane and the four methyl carbon atoms bound to each phosphorus atom is disordered in **5b**. In Figure 2, the major orientation (96 %) is represented. All non-hydrogen atoms (except for the minor parts of the disordered moieties in the cases of **4b** and **5b**) were refined anisotropically. The final cycles of full-matrix least-squares refinement were based on 16756 (**4b**) and 14928 (**5b**) observed reflections (all data) and 761 (**4b**) and 821 (**5b**) variable parameters, respectively. 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-169659 (**4b**) and -169660 (**5b**). 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 First Stable Phosphabismuthene\*\*

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There has been much interest in doubly bonded compounds between Group 15 elements, that is, heavier congeners of azo compounds, since the first isolation of a stable diphosphene, Mes\*P=PMe\* (Mes\* = 2,4,6-tri-*tert*-butylphenyl), by Yoshifuji et al. in 1981.<sup>[1]</sup> In 1980s, several examples of kinetically stabilized diphosphenes (RP=PR)<sup>[2]</sup> and diarsenes (RAS=AsR)<sup>[3]</sup> have been synthesized and fully characterized. In contrast, much heavier analogues, that is, distibene (RSb=SbR)<sup>[4]</sup> and dibismuthene (RBi=BiR),<sup>[5]</sup> have only been reported very recently by us, where the first isolation of stable distibene and dibismuthene was achieved by taking advantage of an efficient steric protection group, 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl (denoted as Tbt) (Scheme 1).<sup>[6]</sup> Later on,

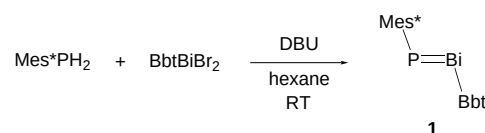


Scheme 1. Some steric protection groups.

Power and co-workers also described the syntheses of another series of distibenes and dibismuthene containing bulky 2,6-Ar<sub>2</sub>C<sub>6</sub>H<sub>3</sub> groups (Ar = mesityl or 2,4,6-triisopropylphenyl).<sup>[7]</sup> Thus, homonuclear doubly bonded systems between heavier Group 15 elements are no longer imaginary species even in the case of bismuth, and the next target molecules are heteronuclear doubly bonded systems, which may be key compounds of great importance in the systematic elucidation of the intrinsic nature of low-coordinate compounds of

heavier main group elements. While some examples of phospharsenes and phosphastibenes are reported,<sup>[8,9]</sup> no heteronuclear double bonds between bismuth and the other Group 15 elements have been described probably because of the weakness of  $\pi$  bond between Bi and another atom due to the difference of the size of the p orbitals. Very recently, however, we succeeded in the synthesis of the first stable stibabismuthene (BbtSb=BiBbt),<sup>[10]</sup> which is the first example of a heteronuclear doubly bonded system containing a bismuth atom, by taking advantage of a new type of steric protection group, 2,6-bis[bis(trimethylsilyl)methyl]-4-[tris(trimethylsilyl)methyl]phenyl (denoted as Bbt).<sup>[11]</sup> Herein, we report the first synthesis of a stable phosphabismuthene, that is, a novel doubly bonded system between phosphorus and bismuth atoms, in which the exceedingly different size of p orbitals is overcome.

The condensation reaction of BbtBiBr<sub>2</sub> with Mes\*PH<sub>2</sub> in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hexane at room temperature afforded a deep orange powder (Scheme 2), the <sup>31</sup>P NMR spectrum of which showed a broad



Scheme 2. Synthesis of phosphabismuthene **1**.

singlet at  $\delta = 612$  along with a small peak for Mes\*PH<sub>2</sub> ( $\delta = -130$ ). Since the low-field chemical shift of  $\delta = 612$  is characteristic of a low-coordinate phosphorus atom, this result strongly suggests the formation of phosphabismuthene **1** in this reaction. In addition, the broadening of the signal, which is considered to be due to the 9/2 nuclear spin of the adjacent Bi atom, is also regarded as an evidence for the P=Bi double bond of **1**. The yield of **1** was estimated to be 91 % on the basis of a comparison of the integrals of the <sup>1</sup>H NMR signals compared with those of TbtH added as an internal standard. Although phosphabismuthene **1** was very difficult to purify by chromatographic separation owing to its extreme high reactivity toward moisture and air, recrystallization of the orange powder from hexane at  $-40^\circ\text{C}$  afforded **1**·0.5 hexane as green single crystals. It is noteworthy that compound **1** is not only a new member of a novel class of heteronuclear doubly bonded systems between heavier Group 15 elements but also the first example of a stable species with a double bond between the third and sixth row main group elements.

The molecular structure of **1** was determined by X-ray crystallographic analysis (Figure 1).<sup>[12]</sup> This molecule has a *trans* configuration with a C–Bi–P–C torsion angle of  $179.79(9)^\circ$ . The length of the P–Bi bond of **1** is 2.4541(6) Å, which is the midpoint between the E–E bond lengths of the corresponding diphosphene (Mes\*P=PMe\* (**2**), 2.034(2) Å)<sup>[1]</sup> and dibismuthenes (TbtBi=BiTbt (**3**), 2.8206(8) Å)<sup>[5]</sup> and BbtBi=BiBbt (**4**), 2.8699(6) Å)<sup>[13]</sup>. This P–Bi bond length is about 8 % shorter than the sum of the covalent radii of the phosphorus and bismuth atoms (2.66 Å)

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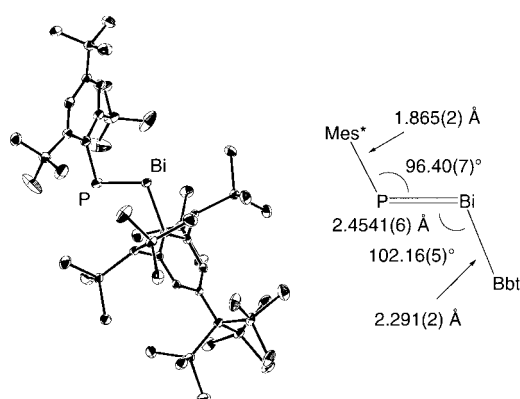


Figure 1. Left: Molecular structure of **1** (ORTEP drawing; thermal ellipsoid plot (50% probability)). The fragment of solvated hexane was omitted for clarity. Right: Schematic drawing of **1** with some selected bond lengths and angles.

as well as the E=E bond lengths of the doubly bonded system between heavier Group 15 elements, which are known to be about 8% shorter than the corresponding E–E single bonds.<sup>[14]</sup> On the other hand, the Bi–P–C and P–Bi–C angles of **1** were found to be 96.40(7)° and 102.16(5)° respectively. The considerably wider angle at the Bi atom than that at the P atom may be surprising, because the angles at pnictogens generally become smaller with increasing atomic number (from N to Bi). It is well known that the heavier pnictogens have a stronger tendency to maintain the (ns)<sup>2</sup>(np)<sup>3</sup> valence electron configuration because of the larger size difference and energy gap between the valence s and p orbitals.<sup>[15]</sup> The results of theoretical calculations for RP=BiR' systems,<sup>[16]</sup> which are summarized in Table 1, lead us to a reasonable understanding. All the optimized structures for RP=BiR' systems show very similar bond lengths for their P–Bi bond

Table 1. Calculated structures of phosphabismuthenes.<sup>[16]</sup>

| RP=BiR'                   |          | Angle [°] |         | Length [Å] |
|---------------------------|----------|-----------|---------|------------|
|                           |          | R–P–Bi    | P–Bi–R' |            |
| Ph–P=Bi–Ph <sup>[a]</sup> | <b>5</b> | 97.0      | 96.6    | 2.427      |
| Mes*–P=Bi–Bbt             | <b>1</b> | 95.3      | 104.4   | 2.440      |
| Bbt–P=Bi–Mes*             | <b>6</b> | 104.8     | 94.1    | 2.442      |
| H–P=Bi–Bbt                | <b>7</b> | 90.0      | 103.0   | 2.428      |

[a] The phenyl groups are fixed perpendicularly to the C–P–Bi plane.

(ca. 2.43 Å), which are almost consistent with the experimentally obtained P–Bi bond lengths of **1**. By contrast, the bond angles at the phosphorus and bismuth atoms vary in these systems. The optimized geometry of PhP=BiPh (**5**) showed no distinct difference between angles at the phosphorus atom (97.0°) and the bismuth atom (96.6°) in contrast to the experimentally obtained values of **1**. On the other hand, a theoretically optimized structure of the more sterically congested system, Mes\*P=BiBbt (**1**), was found to have structural parameters (95.3° for P and 104.4° for Bi) almost the same as the experimentally obtained values. The optimized structural parameters for the reversibly substituted model system BbtP=BiMes\* (**6**) showed a widened angle at the P atom (104.8°) and almost the same angle at the Bi atom

(94.1°) as that of PhP=BiPh (**5**). In addition, the P–Bi–C angle of HP=BiBbt (**7**) system was also found to be widened to 103.1°, which is almost the same value as that of **1**. These results indicate that the wider angle at the Bi atom determined from the X-ray crystallographic analysis of **1** is probably due to the steric repulsion not between the substituents (Mes\* and Bbt group) but between the bulky Bbt group and the central P=Bi moiety.

The UV/Vis spectrum of **1** in hexane shows characteristically red-shifted absorption maxima at 455 ( $\epsilon$  10000), 540 (sh, 1000), and 670 (300) nm, while the previously known heavier congeners of azo compounds show only two absorption maxima corresponding to the symmetry-allowed  $\pi \rightarrow \pi^*$  and symmetry-forbidden  $n \rightarrow \pi^*$  electron transitions at wavelengths longer than 300 nm in all cases. The  $\lambda_{\max}$  value of 455 nm, which is attributable to the  $\pi \rightarrow \pi^*$  transition of the P=Bi chromophore, lies in the middle between the  $\pi \rightarrow \pi^*$  transition of Mes\*P=PMes\* (**2**;  $\lambda_{\max}$  340 nm ( $\epsilon$  7690))<sup>[1]</sup> and that of BbtBi=BiBbt (**4**;  $\lambda_{\max}$  537 nm ( $\epsilon$  6000)).<sup>[13]</sup> Although the latter two  $\lambda_{\max}$  values observed for **1** (540 and 670 nm) are most likely due to the  $n \rightarrow \pi^*$  transitions and one of them at 540 nm is reasonably found in the middle between the  $\lambda_{\max}$  value of **2** (460 nm ( $\epsilon$  1360)) and that of **4** (670 nm (sh,  $\epsilon$  20)), another one at 670 nm lies at a strangely longer wavelength. Although we have no clear explanation for the additional  $n \rightarrow \pi^*$  transition observed in longer wavelength region for **1**, it could be consistent with the assumption that heteronuclear doubly bonded systems between heavier Group 15 elements should have two weak  $n \rightarrow \pi^*$  transitions due to two chemically distinct lone pairs on the phosphorus and the bismuth atoms in addition to one strong  $\pi \rightarrow \pi^*$  transition. These outcomes for phosphabismuthene **1** discussed above are also of great importance for understanding the spectroscopic properties of BbtSb=BiBbt, which we reported previously.<sup>[10]</sup>

Thus, **1** features a double bond between the phosphorus and the bismuth atom in the solid state and even in solution, as suggested by the NMR and UV/Vis spectra and X-ray crystallographic analysis. Further investigation of the physical and chemical properties of **1** is currently in progress. Now, as for heavier Group 15 elements, not only the homonuclear doubly bonded compounds but also the heteronuclear systems have been obtained as stable compounds, even in the case of elements from rows that differ by more than one (i.e. P and Bi), when they are kinetically well stabilized. The concept of kinetic stabilization should be very helpful for the synthesis of unprecedented doubly bonded systems such as As=Sb, As=Bi, Sb=Si, and Bi=Si.

## Experimental Section

**1**: DBU (15.0  $\mu$ L, 0.10 mmol) was added dropwise by means of a syringe to a solution of Mes\*PH<sub>2</sub> (14.7 mg, 0.053 mmol) and BbtBiBr<sub>2</sub> (51.0 mg, 0.051 mmol) in hexane (10 mL) at room temperature (ca. 25 °C). The resulting orange solution was stirred at the same temperature for 14 h. After filtration through Celite, the filtrate was evaporated. The residue (orange powder, 57.0 mg) contained **1** as a main product (0.046 mmol, 91 %, estimated by <sup>1</sup>H NMR spectroscopy by using TbtH as an internal standard), along with a small amount of Mes\*PH<sub>2</sub> and DBU. **1**: m.p. 120.0–121.2 °C (decomp); <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  = 0.25 (s, 36H), 0.40 (s, 27H), 1.41 (s, 9H), 1.68 (s, 2H), 1.70 (s, 18H), 7.58 (s, 2H), 7.84 (s, 2H); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  = 2.29 (q), 6.11 (q), 22.80 (s), 32.96 (q), 33.98 (s), 37.02

(q), 38.46 (s), 40.61 (d), 119.79(d), 128.52 (s), 131.05 (d), 144.59 (s), 150.66 (s), 152.30 (s), 159.59 (s), a signal assignable to *ipso*-<sup>13</sup>C of Bbt group was not observed.; <sup>31</sup>P NMR (121 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  = 612.0; UV/vis (*n*-hexane):  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 455 (10000), 540 (sh, 1000), and 670 nm (300); high-resolution MS (FAB): *m/z*: 1109.5511([*M*+H]<sup>+</sup>), calcd for C<sub>48</sub>H<sub>97</sub>Si<sub>7</sub>PBi 1109.5516. Slow evaporation of a hexane solution of the residue in a refrigerator at -40 °C fixed in a glovebox filled with argon gave green crystals of **1**·0.5 hexane.

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- [12] Crystal data for **1**·0.5 hexane (C<sub>51</sub>H<sub>103</sub>BiPSi<sub>7</sub>): *M<sub>r</sub>* = 1152.91, *T* = 93(2) K, triclinic, *P* $\bar{1}$  (no. 2), *a* = 12.7372(2), *b* = 14.6943(5), *c* = 18.5933(5) Å,  $\alpha$  = 107.5367(14),  $\beta$  = 95.2385(15),  $\gamma$  = 107.9837(5)°, *V* = 3090.27(14) Å<sup>3</sup>, *Z* = 2,  $\rho_{\text{calcd}}$  = 1.239 g cm<sup>-3</sup>,  $\mu$  = 3.044 mm<sup>-1</sup>,  $\lambda$  = 0.71070 Å,  $2\theta_{\text{max}}$  = 50.0, 35 164 measured reflections, 10813 independent reflections, 572 refined parameters, GOF = 1.034, *R*<sub>1</sub> = 0.0201 and *wR*<sub>2</sub> = 0.0483 (*I* > 2 $\sigma$ (*I*)), *R*<sub>1</sub> = 0.0225 and *wR*<sub>2</sub> = 0.0489 (for all data), largest difference peak and hole 1.106 and -0.476 e Å<sup>-3</sup>. 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-168594. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). The intensity data were collected on a Rigaku/MSC Mercury CCD diffractometer. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares procedures on *F*<sup>2</sup> for all reflections (SHELXL-97). All hydrogens were placed using AFIX instructions.
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## Erodible Conducting Polymers for Potential Biomedical Applications\*\*

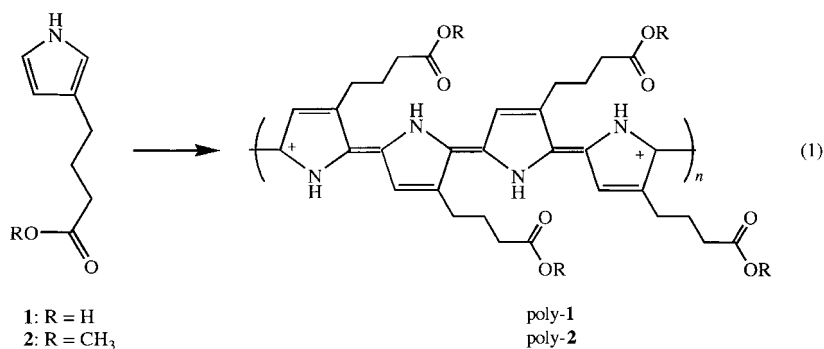
Alexander N. Zelikin, David M. Lynn, Jian Farhadi, Ivan Martin, Venkatram Shastri,\* and Robert Langer\*

Electrically conducting polymers have been investigated for numerous applications, including organic substitutes for metals in electronic circuits,<sup>[1]</sup> coatings for electromagnetic shielding,<sup>[2]</sup> analytical and biological sensing devices,<sup>[3–5]</sup> and as substrates for the manipulation of mammalian cell growth and function.<sup>[6]</sup> From a separate standpoint, the development and application of biodegradable polymers has had a profound impact in numerous medical and surgical applications.<sup>[7]</sup> It occurred to us that the creation of biocompatible, degradable conducting polymers could open the door to a number of new biomedical applications.<sup>[8]</sup> Several groups have reported the synthesis and characterization of conducting poly(thiophene) derivatives containing hydrolyzable ester groups in the polymer backbone.<sup>[9]</sup> However, to our knowledge, the degradability and biocompatibility of these polymers has not been established, and the reduced environmental stability of oxidized polythiophenes could limit their application under physiological conditions.

Of the various electrically conducting polymers, polypyrrole (Ppy) has been the most widely studied material for potential biomedical applications because it is relatively stable to air and water and can be readily synthesized through chemical and electrochemical routes.<sup>[10]</sup> Additionally, Ppy is a suitable substrate for cell attachment and proliferation<sup>[6]</sup> and possesses excellent biocompatibility *in vivo*.<sup>[8, 11]</sup> Our attempts to synthesize biodegradable Ppy derivatives through the incorporation of backbone ester moieties (in analogy to the polythiophenes discussed above) have thus far been unsuccessful because of extensive side reactions accompanying pyrrole coupling chemistry and the generally poor oxidative stability of the requisite oligopyrrole intermediates. Herein, we report an alternative strategy for the design of erodible Ppy materials based on the chemical and electrochemical polymerization of  $\beta$ -substituted pyrrole monomers containing ionizable and/or hydrolyzable side groups [Eq. 1]. These polymers can be fabricated into conductive materials that erode slowly under physiological conditions and support the growth, proliferation, and differentiation of primary human cells in *in vitro* cell culture assays.

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We recently reported the synthesis of carboxylic acid functionalized pyrrole monomer **1**.<sup>[12]</sup> Direct esterification of compound **1** by reflux in methanol in the presence of phenylsulfonic acid afforded methyl ester functionalized monomer **2** in 80% yield. Both monomers underwent oxidative electrochemical polymerization and ferric chloride mediated chemical polymerization to yield conductive thin films and colloidal dispersions [poly-**1** and poly-**2**, Eq. 1]. In contrast to the insoluble cross-linked polymer deposits typically obtained from the oxidative polymerization of pyrrole, poly-**2** was completely soluble in common organic solvents such as THF and chloroform. Poly-**1** was insoluble in organic solvents, but was sparingly soluble in water. The solubility of these polymers suggested that they were not extensively cross-linked, presumably because of the presence of the  $\beta$ -substituents that prevent the cross-linking at this position. The sheet resistance of thin films prepared from poly-**1** was 300 ( $\pm$ 100)  $\Omega$ , which is consistent with literature values for  $\beta$ -substituted polypyrroles.<sup>[10, 13]</sup>

In view of the low solubility of poly-**1** in water, we hypothesized that thin films formed from poly-**1** might undergo a gradual erosion process under physiological conditions in a manner approximating the behavior of conventional biodegradable polymer systems. To test this hypothesis, we incubated thin films of poly-**1** in acetate (pH 5.0), HEPES (pH 7.2 HEPES = 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid) and TAE (pH 8.2; TAE = tris(hydroxymethyl)aminomethane acetate, 10 mM ethylenediaminetetraacetate) buffers and investigated their erosion/dissolution profile at 37 °C as a function of pH value. Thin films deposited on iridium tin oxide (ITO) glass dissolved within 24 hours at pH 8.2, but dissolved more slowly at pH 5. Intermediate dissolution rates were observed at pH 7.2. Unfortunately, the deterioration of film quality over time, coupled with the tendency of the films to detach from the ITO substrates and float, prevented a quantitative analysis of the erosion process over an extended period of time.

To facilitate a more quantitative analysis, we prepared pressed pellets of chemically polymerized poly-**1** (20 mg, diameter = 8 mm, thickness = 0.5 mm) and followed the erosion/dissolution of polymer by UV/Vis spectroscopy in acetate (pH 5.0), HEPES (pH 7.2), and TAE (pH 8.2) buffers (see Experimental Section). As shown in Fig-

ure 1, the erosion rate of pellets at pH 7.2 was twice the rate of erosion at pH 5.0, and the rate was dramatically enhanced under alkaline conditions. Pressed pellets formed from hydrophobic methyl ester functionalized poly-**2** eroded much more slowly than their acid-functionalized counterparts (50 mg, diameter = 8 mm, thickness = 1 mm) at pH 7.2. As shown in Figure 2, the mass loss from pellets of poly-**1** was 27% after 80 days of incubation at 37 °C, while the mass loss from pellets of poly-**2** was 6%. These results parallel an increase in pyrrole oligomer concentration in solution over time (as determined by UV/Vis spectroscopy, Figure 2). The disparity in the erosion/dissolution rates between poly-**1** and poly-**2** suggests a means of tailoring erosion rates through judicious copolymerization of both

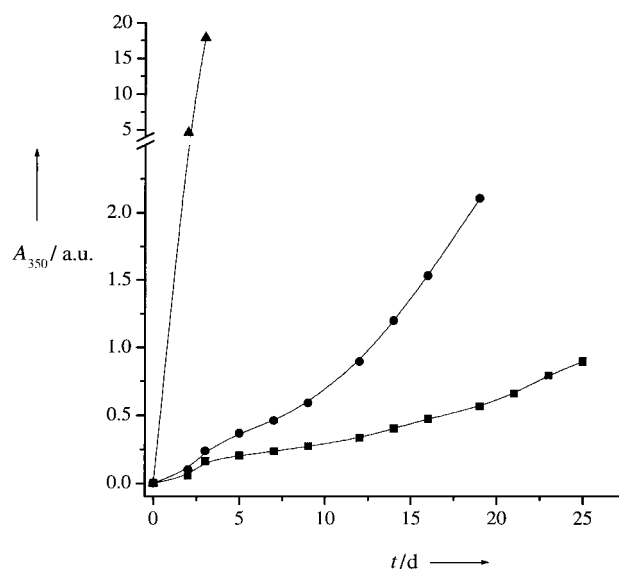


Figure 1. Dissolution of pressed pellets of poly-**1**, monitored by UV/Vis spectroscopy, at different pH: 8.2 ( $\blacktriangle$ ), 7.2 ( $\bullet$ ), and 5.0 ( $\blacksquare$ )

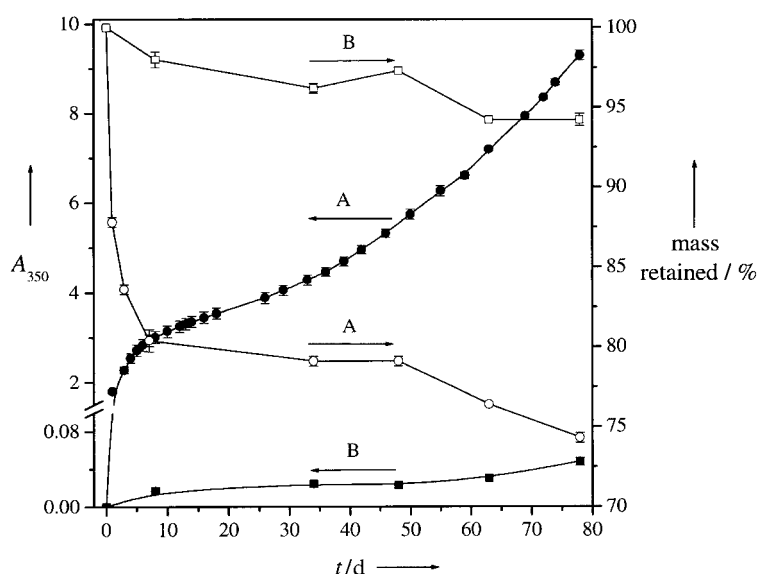


Figure 2. Dissolution of pressed pellets of poly-**1** (A) and poly-**2** (B), as monitored by solution UV/Vis absorbance ( $\bullet$ ,  $\blacksquare$ ) and mass loss ( $\circ$ ,  $\square$ ).

hydrophilic and hydrophobic monomers.<sup>[14]</sup> Unfortunately, the surface roughness arising from erosion (scanning electron microscopy, data not shown), prevented a detailed study of the conductivity of the pellets as a function of degradation time; the design of a system to address this issue is currently underway. The sheet resistance of thin films prepared from poly-1 rises slightly upon incubation in water, and reaches a plateau at approximately 700 ( $\pm 200$ )  $\Omega$  after two days. These data indicate that the films remain conductive under aqueous or water-equilibrated conditions. The resistance of these equilibrated films is similar to that of films formed from Ppy previously used for the stimulation of cells and tissue.<sup>[8]</sup>

We also carried out cytocompatibility studies on thin films of poly-1 using primary human bone-marrow derived mesenchymal progenitor cells (MPCs) as a model cell system. All seeded cells attached to the substrate and proliferated at an average rate of 0.63 doublings per day, comparable to that measured for cells growing on tissue-culture-treated plastic.<sup>[15]</sup> MPCs cultured for nine days on the erodible Ppy substrate in medium promoting osteogenic differentiation progressed towards the osteoblast lineage, as assessed by the increased mRNA expression of collagen Type I (1.8-fold), bone sialoprotein (2.4-fold), and osteopontin (19.2-fold; Figure 3).

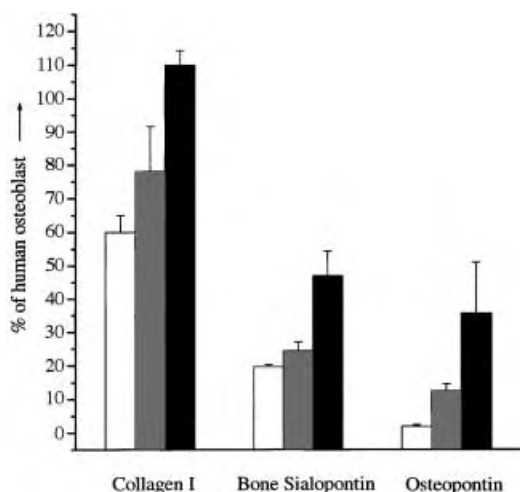


Figure 3. mRNA expression levels of osteoblast-related markers (collagen Type I, bone sialoprotein, and osteopontin) in mesenchymal progenitor cells grown on thin films of poly-1, before (white) and after exposure to soluble osteogenic stimuli for five (gray) or nine (black) days. The values, quantified and normalized to the amounts of 18-S rRNA (housekeeping gene) by using real-time reverse transcriptase polymerase chain reaction (RT-PCR), are expressed as a percentage of those measured in human osteoblasts.

Although additional experiments *in vivo* will be required to more accurately determine the biocompatibility of the developed polymers, these results demonstrate the potential for erodible Ppy-based materials as cell substrates in biomedical applications. The conductive nature of Ppy has been shown to allow interactive control over cell shape, differentiation, and function.<sup>[8, 11, 16]</sup> Ongoing studies are aimed towards influencing the behavior of cells cultured on erodible Ppy substrates through the application of magnetic fields and/or electrical currents.

## Experimental Section

4- $\beta$ -pyrrolylbutyric acid (**1**) was prepared as previously described.<sup>[12]</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 1.9 (m, 2H), 2.4 (t, 2H), 2.55 (t, 2H), 6.1 (s, 1H), 6.4 (s, 1H), 6.72 (s, 1H).

Methyl-4- $\beta$ -pyrrolylbutyrate (**2**): **1** (2.0 g, 13 mmol) in methanol (25 mL) was heated under reflux overnight in the presence of catalytic amounts of phenylsulfonic acid. The reaction mixture was poured onto ice cold water (200 mL) and extracted with diethyl ether (5  $\times$  25 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent followed by a silica column chromatography (eluent ethyl acetate:hexane = 1:3) and removal of solvents gave 1.6 g of a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 1.9 (m, 2H), 2.4 (t, 2H), 2.55 (t, 2H), 3.64 (s, 3H), 6.1 (s, 1H), 6.4 (s, 1H), 6.72 (s, 1H).

Chemical polymerization: Monomer **1** (2.52 g, 16.5 mmol) and tetrabutylammonium *p*-toluenesulfonate (6.8 g, 16.5 mmol) were dissolved in acetonitrile (25 mL) and mixed with an equal volume of acetonitrile charged with ferric chloride (5.36 g, 33 mmol). The mixture was stirred vigorously for 20 min, then poured onto ice-cold water (500 mL). The precipitate was collected, washed with water (5  $\times$  50 mL), and dried under vacuum. Polymer **2** was synthesized in an analogous manner. Gel permeation chromatography (GPC) analysis of polymer **2** (THF, 0.1 M piperidine) showed that the sample primarily consists of oligomers ( $M_n$  = 1700,  $M_w$  = 3200 relative to monodisperse polystyrene standards). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 1.9 (m, 2H), 2.4 (t, 2H), 2.55 (t, 2H), 6.1–7.9. Elemental analysis of the polymers showed trace amounts of Cl (0.14%) and Fe (0.15%).

Electrochemical polymerization: **1** was electrochemically deposited onto indium tin oxide (ITO) coated glass slides from a 1 M solution in acetonitrile containing 0.5 M of tetrabutylammonium tetrafluoroborate by passing 1 Coulomb of electrical current at a constant potential (1.0 V vs Ag/AgCl reference electrode).

pH Dependent degradation: Pressed pellets formed from poly-1 were incubated at 37 °C in 2 mL of the media with the desired pH value (0.01 M acetate buffer, pH 5.0; 0.01 M HEPES buffer, pH 7.2; 1  $\times$  TAE buffer, pH 8.2). Media was changed and subsequently analyzed with UV/Vis spectroscopy every 2–4 days.

Degradation of pressed pellets: Pressed pellets were placed into HEPES buffer (10 mL, 0.1 M; pH 7.2) and incubated at 37 °C on an orbital shaker. For experiments employing poly-1, buffer media was removed for absorbance measurements and replaced with fresh media every 2–5 days. As pellets formed from poly-2 degraded more slowly than poly-1, buffer media was collected and analyzed every 7–14 days. The mass loss of the pellets was analyzed at selected time points by removing the incubation media, washing the pellets with de-ionized water (3  $\times$  5 mL), and subsequently freeze-drying each pellet. All experiments were performed in triplicate.

Cell culture: Culture medium (CM) was Dulbecco's modified Eagle medium with 10% fetal bovine serum (LOT40G2470J, Gibco BRL Life Technology, Basel, CH), D-glucose (4.5 mg/mL), nonessential amino acids (0.1 mM), sodium pyruvate (1 mM), HEPES buffer (100 mM), penicillin (100 U/mL), streptomycin (100  $\mu$ g/mL), and L-glutamine (0.29 mg/mL). Bone marrow aspirates were obtained during routine orthopedic surgical procedures involving exposure of the iliac crest, after informed consent. Nucleated cells were isolated using a density gradient solution (Histopaque, Sigma Chemical, Buchs, CH), plated at a density of 3,000 cells cm<sup>-2</sup> in CM supplemented with fibroblast growth factor-2 (5 ng/mL; R&D Systems, Wiesbaden, D) and dexamethasone (10 nM; Sigma) and cultured in a humidified 37 °C/5% CO<sub>2</sub> incubator.<sup>[15]</sup> MPC were selected on the basis of adhesion and proliferation on the plastic substrate. After about 10 days, upon reaching subconfluency, MPC were detached using 0.25% trypsin/1 mM EDTA (EDTA = ethylenediaminetetraacetate) and plated on glass slides coated with the polymer **1**, at a density of 6,000 cells cm<sup>-2</sup>. Cells were cultured in medium known to promote MPC osteogenic differentiation, which consisted of CM supplemented with dexamethasone (10 nM), L-ascorbic acid-2-phosphate (0.1 mM), and  $\beta$ -glycerophosphate (10 mM).<sup>[17]</sup> Cultures were harvested at timed intervals (5 and 9 days) and assessed for DNA content and mRNA analysis as described below.

Cell proliferation: The DNA content of MPC cultures was assessed using the CyQuant kit (Molecular Probes, Eugene, Oregon). MPC proliferation

rate was defined as the number of doublings between day 5 and day 9 (determined as the logarithm in base 2 of the increase in the DNA amount) divided by the elapsed time (4 days).

Real-Time quantitative RT-PCR: RNA was extracted from cell layers using Trizol (Life Technologies, Basel, CH) according to the single step acid-phenol guanidinium method,<sup>[18]</sup> treated with DNase I using the DNA-free kit (AMS Biotechnology Ltd, CH) and transcribed into cDNA by using random hexamers (Catalys AG, CH) and Stratascript reverse transcriptase (Stratagene, NL). Real-time RT-PCR reactions were performed and monitored using an ABI Prism 7700 sequence detection system (Applied Biosystems, Rotkreuz, Switzerland). In the same reaction, cDNA samples were analyzed both for the gene of interest and the reference housekeeping gene (18-S rRNA), by using a multiplex approach (Perkin Elmer User Bulletin No. 2). The probe for 18-S rRNA was fluorescently labeled with VIC and TAMRA (Applied Biosystems), whereas probes for the genes of interest were labeled with 6-carboxy-fluorescein (FAM) and TAMRA. The efficiency of each set of primers and probes, assessed as previously described,<sup>[19]</sup> was always higher than 90%. Primers were purchased from Microsynth (Balgach, CH) and probes were from Perkin-Elmer or Eurogentech (Seraing, B).

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## Characterization of C<sub>2</sub> (C<sub>x</sub>H<sub>y</sub>) Intermediates from Adsorption and Decomposition of Methane on Supported Metal Catalysts by in situ INS Vibrational Spectroscopy\*\*

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Conversion of methane into higher hydrocarbons is a process of enormous technological importance, which would benefit from a better understanding of the nature of the surface intermediates formed during methane activation. Currently methane is converted into hydrocarbons mainly by an indirect route<sup>[1,2]</sup> via syn gas<sup>[3]</sup> as the intermediate. Alternative routes, such as oxidative coupling of methane<sup>[4–7]</sup> over metal oxide catalysts and methane homologation<sup>[8–10]</sup> on transition metal catalysts have also been extensively investigated. In a previous study we<sup>[11]</sup> have observed the formation of various C<sub>x</sub>H<sub>y</sub> surface intermediate species after methane decomposition on single-crystal Ru(0001) and Ru(1120) model catalysts, observed by high-resolution electron energy loss spectroscopy (HREELS). In this study we used INS to investigate the surface intermediate species formed during the decomposition of methane on Ru/Al<sub>2</sub>O<sub>3</sub> and Ni/SiO<sub>2</sub> catalysts. We relate these findings to our previous work on idealized single-crystal model catalysts. The present work represents a step in the effort to bridge the gap between surface science and real-world catalysts in terms of the type of material and pressure used. Inelastic neutron scattering (INS)<sup>[12–14]</sup> vibrational spectroscopy is a technique that can be directly applied to high surface-area catalysts from ambient to high pressures. This method can also provide accurate quantitative information, has high sensitivity to hydrogenous species, and is not limited by the selection rules of other vibrational spectroscopies.

Herein we report the first experimental evidence of the formation of ethylidyne, vinylidene, and methylidyne (C<sub>x</sub>H<sub>y</sub>) species from methane on supported metal catalysts. Shown in Figure 1 is the difference INS vibrational spectrum after methane decomposition on Ru/Al<sub>2</sub>O<sub>3</sub>. The rather modest resolution, especially at higher frequencies, and poor statistics are the result of having to use a difference spectrum and of the relatively small amount of H in the sample. Nonetheless, the

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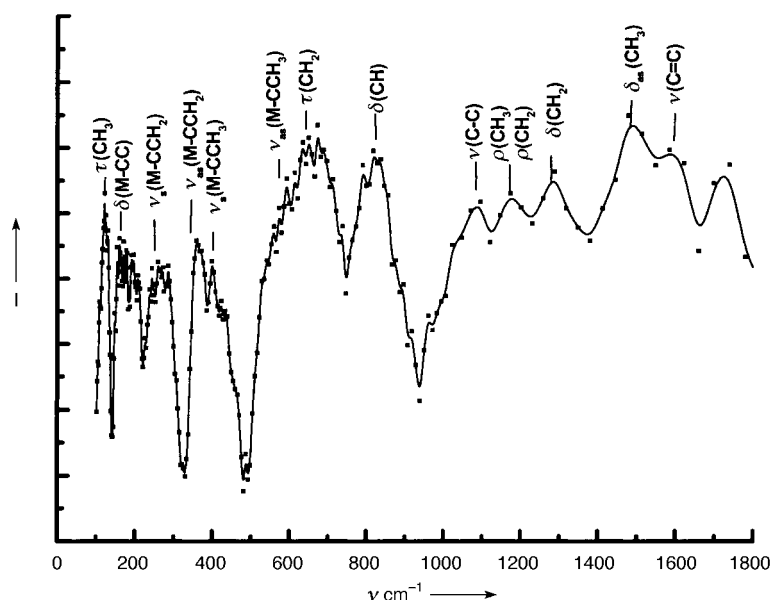


Figure 1. INS spectrum obtained after methane decomposition over Ru/Al<sub>2</sub>O<sub>3</sub> at 250 °C, some tentative assignments are shown. (The line is drawn to guide the eye).

spectrum clearly reveals the presence of the C<sub>2</sub> species in addition to CH. Our assignments are made with reference to work on model compounds as well as the previous HREELS study<sup>[11]</sup> on single-crystal surfaces. Thus, we tentatively assign the bands at approximately 120, 400, 570, 1085, 1165, 1485 cm<sup>-1</sup> to modes of the ethylidyne species, namely  $\tau(\text{CH}_3)$ ,  $\nu_s(\text{M-CCH}_3)$ ,  $\nu_{as}(\text{M-CCH}_3)$ ,  $\nu(\text{C-C})$ ,  $\rho(\text{CH}_3)$ , and  $\delta_{as}(\text{CH}_3)$ , respectively (M is the surface metal atom, namely Ni or Ru). For the vinylidene species we observe bands at 200, 280, 360, 670, 1220, and 1300 and cm<sup>-1</sup> which we attribute to  $\delta(\text{M-CC})$ ,  $\nu_s(\text{M-CCH}_2)$ ,  $\nu_{as}(\text{M-CCH}_2)$ ,  $\tau(\text{CH}_2)$ ,  $\rho(\text{CH}_2)$ , and  $\delta(\text{CH}_2)$ , respectively. Other CH<sub>2</sub> deformation modes are contained in the broad band above 1450 cm<sup>-1</sup> and the  $\nu(\text{C=C})$

mode appears at approximately 1580 cm<sup>-1</sup>. The peak at 830 cm<sup>-1</sup> may be assigned to the CH bending mode of methylidyne. M-C stretching modes for methylidyne should also be observable and are assumed to be contained in the broad bands below 500 cm<sup>-1</sup>. Computational studies are in progress to aid in the detailed assignment of the M-C stretching and other modes of these intermediate species. The observation of the methylidyne species (CH) at 830 cm<sup>-1</sup> is in good agreement with earlier studies which reported that other methyl intermediates decompose below 202 °C to produce the CH species.<sup>[15]</sup> Summarized in Table 1 are the INS vibrational frequencies and tentative mode assignments for the three C<sub>x</sub>H<sub>y</sub> (vinylidene, ethylidyne, and methylidyne) species on the supported Ru and Ni catalysts. It is worth noting that we find features similar to those on Ru/Al<sub>2</sub>O<sub>3</sub> for the Ni/SiO<sub>2</sub> catalysts although the ethylidyne species has rarely been observed on Ni surfaces.<sup>[16]</sup> Our assignments of modes of the vinylidene and ethylidyne species are in excellent agreement with our

previous work on Ru(1120) model catalysts<sup>[11]</sup> (Table 1).

At the higher decomposition temperature of 325 °C we find that the bands assigned to the ethylidyne species decrease in intensity relative to those of vinylidene, most notably  $\tau(\text{CH}_3)$ ,  $\nu_s(\text{M-CCH}_3)$ ,  $\nu_{as}(\text{M-CCH}_3)$ ,  $\nu(\text{C-C})$ , and the deformation modes of  $\delta(\text{CH}_3)$ . For the vinylidene species the intensities of  $\nu_s(\text{M-CCH}_2)$ ,  $\nu_{as}(\text{M-CCH}_2)$ ,  $\delta_s(\text{CH}_2)$ , and  $\nu(\text{C=C})$  are higher at 325 °C which clearly suggests that this C<sub>2</sub> intermediate is more stable at higher temperatures than ethylidyne. This result is in good agreement with methane decomposition studies on Ru(1120)<sup>[11, 17]</sup> where the ethylidyne species was found to exist only at low temperature and was found to transform to vinylidene species on heating. Experimental

Table 1. INS vibrational frequencies [cm<sup>-1</sup>] and mode assignments for various C<sub>x</sub>H<sub>y</sub> intermediates on supported metal (Ni, Ru) catalysts, single-crystal surfaces (HREELS), and model compounds (IR).

| Methylidyne                           |                   | Surface           |                          |                                                    |                                                                                        |                                                                                        |
|---------------------------------------|-------------------|-------------------|--------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Mode assignment                       | Ni <sup>[a]</sup> | Ru <sup>[a]</sup> | Ru(1120) <sup>[11]</sup> | Ni(111) <sup>[18]</sup>                            | [Ru <sub>3</sub> (μ <sub>3</sub> CH)H <sub>3</sub> (CO) <sub>9</sub> ] <sup>[23]</sup> |                                                                                        |
| δ(CH)                                 | 890               | 830               | 830                      | 790                                                | 894                                                                                    |                                                                                        |
| Vinylidene                            |                   | Surface           |                          |                                                    |                                                                                        |                                                                                        |
| Mode assignment                       | Ni <sup>[a]</sup> | Ru <sup>[a]</sup> | Ru(1120) <sup>[11]</sup> | Ru(0001) <sup>[11]</sup>                           | O/Ru(0001) <sup>[19]</sup>                                                             | [Os <sub>3</sub> H <sub>2</sub> (CCH <sub>2</sub> )(CO) <sub>9</sub> ] <sup>[20]</sup> |
| δ(M-CC)                               | 184               | 200               |                          |                                                    |                                                                                        |                                                                                        |
| ν <sub>s</sub> (M-CCH <sub>2</sub> )  | 283               | 280               |                          |                                                    |                                                                                        | 255                                                                                    |
| ν <sub>as</sub> (M-CCH <sub>2</sub> ) | 375               | 360               | 345                      |                                                    | 455                                                                                    | 311                                                                                    |
| τ(CH <sub>2</sub> )                   | 672               | 670               |                          |                                                    |                                                                                        |                                                                                        |
| ρ(CH <sub>2</sub> )                   | 1260              | 1220              |                          |                                                    |                                                                                        |                                                                                        |
| δ(CH <sub>2</sub> )                   | 1310              | 1300              | 1410                     | 1395                                               | 1435                                                                                   | 1328                                                                                   |
| ν(C=C)                                | 1600              | 1580              | 1620                     | 1160                                               | 1435                                                                                   | 1467                                                                                   |
| Ethylidyne                            |                   | Surface           |                          |                                                    |                                                                                        |                                                                                        |
| Mode assignment                       | Ni <sup>[a]</sup> | Ru <sup>[a]</sup> | Pt black <sup>[21]</sup> | Co <sub>3</sub> -C-CH <sub>3</sub> <sup>[22]</sup> |                                                                                        |                                                                                        |
| δ(M-CC)                               | 184               | 200               |                          | 220                                                |                                                                                        |                                                                                        |
| τ(CH <sub>3</sub> )                   | 125               | 120               |                          |                                                    |                                                                                        |                                                                                        |
| ν <sub>s</sub> (M-CCH <sub>3</sub> )  | 432               | 400               | 400                      | 403                                                |                                                                                        |                                                                                        |
| ν <sub>as</sub> (M-CCH <sub>3</sub> ) | 605               | 570               | (645)                    | 548                                                |                                                                                        |                                                                                        |
| ν <sub>as</sub> (C-C)                 | 1040              | 1085              | 1130                     | 1162                                               |                                                                                        |                                                                                        |
| ρ(CH <sub>3</sub> )                   | 1184              | 1165              | 985                      | 1004                                               |                                                                                        |                                                                                        |
| δ <sub>as</sub> (CH <sub>3</sub> )    | 1477              | 1485              |                          | 1420                                               |                                                                                        |                                                                                        |

[a] The present work.



investigations are in progress to acquire further insights regarding the nature of the intermediates under various reaction conditions.

## Experimental Section

Methane decomposition was carried out for 4 h on pre-reduced samples of 10% Ni/SiO<sub>2</sub> and 10% Ru/Al<sub>2</sub>O<sub>3</sub> at 250° and 325 °C in separate reactors. Each of these was subsequently quenched in a liquid-nitrogen bath. The reactors were then mounted in a closed-cycle refrigerator and INS spectra were collected at –253 °C on the filter difference spectrometer (FDS) instrument at the Lujan Center at Los Alamos National Laboratory. Data were treated by deconvolution of the instrumental resolution function<sup>[24]</sup> and subtraction of spectra of identical starting samples. Some of the experiments were repeated and an excellent reproducibility was observed.

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## Real-time Observation of the H/D Exchange Reaction between Ethylene and Hydrogen on Pt(111)\*\*

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Adsorption and reactions of small hydrocarbon molecules on well-characterized metal single-crystal surfaces have been extensively studied to understand heterogeneous catalysis on a molecular level and design more effective catalysts.<sup>[1]</sup> Deuterated hydrocarbons are frequently used in surface-science studies of hydrocarbon reactions on metal and metal-oxide surfaces. Reaction mechanisms of surface reactions can be better understood by observing H/D reaction products and the kinetic isotope effect. The H/D exchange products on the surface have been analyzed using several different techniques including thermal desorption spectroscopy (TPD), laser induced desorption (LID), secondary ion mass spectroscopy (SIMS), and vibration spectroscopy. The H/D exchange product distribution is often difficult to determine reliably if a molecule undergoes multiple H/D substitution. The H/D substituted molecules are too similar in their spectroscopic features to identify accurately by using vibration spectroscopy. SIMS, TPD, and LID data are often very confusing because of the fragmentation of molecules on the surface or in a mass spectrometer. Fragmentation makes it difficult to quantitatively identify multiply deuterated hydrocarbon species on the surface.

We investigated the reaction of C<sub>2</sub>D<sub>4</sub> and H on a Pt(111) surface using a Cs<sup>+</sup>-ion reactive ion scattering (RIS) method. We successfully identified C<sub>2</sub>D<sub>4-x</sub>H<sub>x</sub> (x = 0–4) species on the surface and observed their concentration change in real time in the temperature range of 200–300 K.

The Cs<sup>+</sup> RIS technique was shown to be an effective method to monitor molecules on surfaces. The experimental details and operating principle for the RIS method can be found elsewhere.<sup>[2]</sup> Briefly, a Cs<sup>+</sup>-ion beam of low energy (10–100 eV) is collided with the surface to be analyzed, and the Cs<sup>+</sup>-molecule cluster ions emitted from the surface are analyzed by a mass spectrometer. The Cs<sup>+</sup>-molecule cluster ions are formed as the Cs<sup>+</sup>-ion projectiles pick up adsorbed

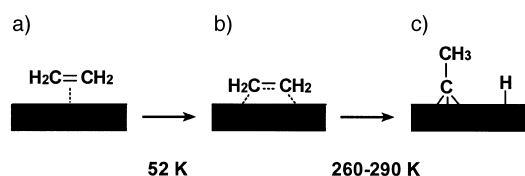
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molecules (reactive scattering process). The greatest advantage of this technique is that molecules are identified in the neutral state and that fragmentation is minimized.

The chemistry of ethylene on Pt(111) has been extensively studied by a variety of surface analysis techniques including TPD,<sup>[3,4]</sup> LID,<sup>[5,6]</sup> SIMS,<sup>[7]</sup> near edge X-ray absorption fine structure (NEXAFS),<sup>[8]</sup> high-resolution electron energy loss spectroscopy (HREELS),<sup>[9]</sup> sum-frequency generation (SFG),<sup>[10]</sup> and reflection absorption infrared spectroscopy (RAIRS).<sup>[11]</sup> The surface reaction steps of ethylene on Pt(111) are shown in Scheme 1, the surface moieties shown have been clearly identified. However, the detailed mechanism for dehydrogenation of di- $\sigma$ -bonded ethylene to ethynylidyne has not been clearly resolved. In addition to the reactions shown in Scheme 1, H/D exchange reactions and desorption of ethylene and ethane take place in the temperature range 220–300 K.



Scheme 1. Surface reaction of ethylene on Pt(111); a)  $\pi$ -bonded ethylene, b) di- $\sigma$ -bonded ethylene, c) ethynylidyne.

We concentrated on the H/D exchange reaction between  $\text{C}_2\text{D}_4$  and H on the surface. Figure 1 shows typical mass spectra of the  $\text{Cs}^+$  RIS products produced from a Pt(111) surface co-adsorbed with H and  $\text{C}_2\text{D}_4$  at two different temperatures. Ethylene is adsorbed molecularly on Pt(111) at 200 K (Scheme 1). The only mass peak observed was 165 amu. This peak corresponds to the  $[\text{CsC}_2\text{D}_4]^+$  ion formed by pickup of  $\text{C}_2\text{D}_4$  from the surface. The absence of fragmented peaks reveals the desorption of intact ethylene.

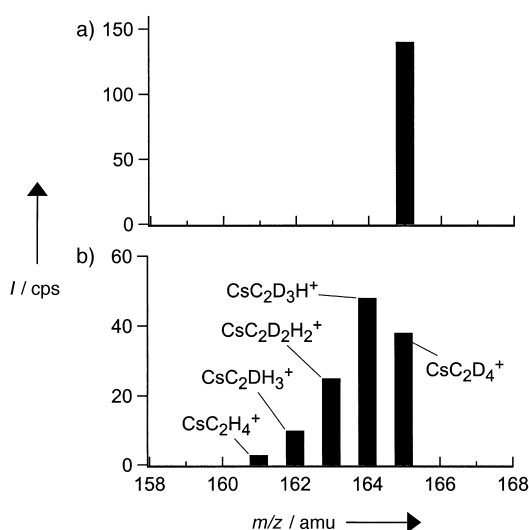


Figure 1. Mass spectra of the RIS products from the Pt(111) surface exposed to  $\text{H}_2$  (5 L) and of  $\text{C}_2\text{D}_4$  (0.5 L) at 200 K. The sample temperature was 200 K (a) and 270 K (b).

At 270 K, the spectrum shows  $\text{CsC}_2\text{D}_3\text{H}$  (164 amu),  $\text{CsC}_2\text{D}_2\text{H}_2$  (163 amu),  $\text{CsC}_2\text{DH}_3$  (162 amu) species. The intensity of  $\text{CsC}_2\text{H}_4$  (161 amu) peak is low but well above the noise level. The intensity distribution truly reflects the relative amounts of corresponding deuterated ethylene on the surface. Note that the ionizer of the mass spectrometer was turned off when we measured  $\text{Cs}^+$ -molecule cluster ions. Thus, we could detect desorbing molecules without cracking by mass spectrometry.

We monitored the change of the intensities of  $\text{C}_2\text{D}_{4-x}\text{H}_x$  ( $x=0-3$ ) species while increasing the surface temperature from 220 K to 295 K (Figure 2). The data show that H/D exchange between ethylene and surface hydrogen takes place even below 230 K. They also show that accumulation of  $\text{C}_2\text{D}_3\text{H}$  is necessary to form  $\text{C}_2\text{D}_2\text{H}_2$ . It is the same for the formation of  $\text{C}_2\text{DH}_3$ . This result implies that the H/D exchange reaction takes place sequentially.

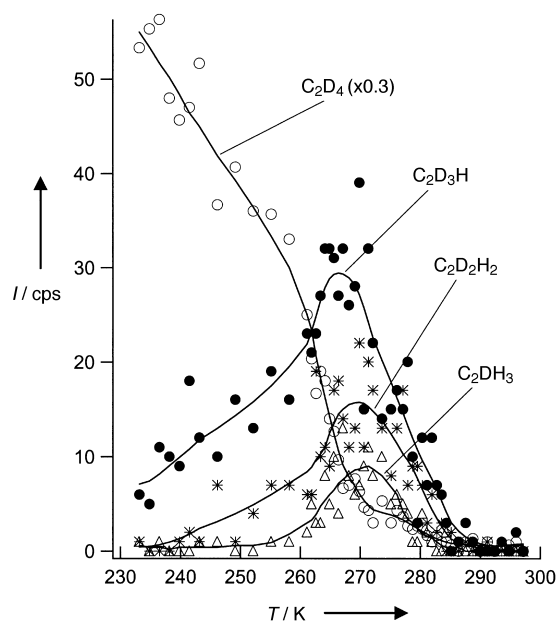


Figure 2. Real-time monitoring of the signal intensities for  $\text{C}_2\text{D}_4$  ( $\circ$ ),  $\text{C}_2\text{D}_3\text{H}$  ( $\bullet$ ),  $\text{C}_2\text{D}_2\text{H}_2$  ( $*$ ), and  $\text{C}_2\text{DH}_3$  ( $\triangle$ ) on Pt(111) during temperature increase. The sample surface was prepared by dosing with  $\text{H}_2$  (5 L) then  $\text{C}_2\text{D}_4$  (0.5 L) at 200 K. The heating rate was  $0.3 \text{ K s}^{-1}$ . Lines drawn to aid the eye.

The intensity of  $\text{C}_2\text{D}_4$  decreased sharply at temperatures higher than 265 K and all of the ethylene species disappeared completely when temperature reached 290 K. This observation reflects decomposition of ethylene to ethynylidyne. Notice that the total amount of  $\text{C}_2\text{D}_{4-x}\text{H}_x$  ( $x=1-4$ ) formed is less than the decrease in the amount of  $\text{C}_2\text{D}_4$ ; this is a result of desorption as ethylene and ethane and decomposition to ethynylidyne. The amount of surface species removed by the  $\text{Cs}^+$ -ion beam itself was estimated to be less than 0.1 % of the total adsorbed species in the whole data collection period.

Even though Figure 2 gives clear indication for progressive H/D exchange, the investigation of the exchange kinetics is complicated because molecular desorption of ethylene and ethane takes place in the temperature range of 240–280 K. To compare their relative amounts exempt from the desorption effect, we plotted the ratio of  $\text{C}_2\text{D}_3\text{H}$  to  $\text{C}_2\text{D}_4$ , and  $\text{C}_2\text{D}_2\text{H}_2$  to

$C_2D_3H$  (Figure 3). Figure 3 shows clearly that the H/D exchange-reaction rate increases abruptly when the surface temperature reaches 260 K. The rate increase for the first H/D exchange ( $C_2D_4 \rightarrow C_2D_3H$ ) is much greater than that for the second one ( $C_2D_3H \rightarrow C_2D_2H_2$ ). The peculiar features of Figure 3 evoke an interpretation that new reaction channels may become operative at 260 K.

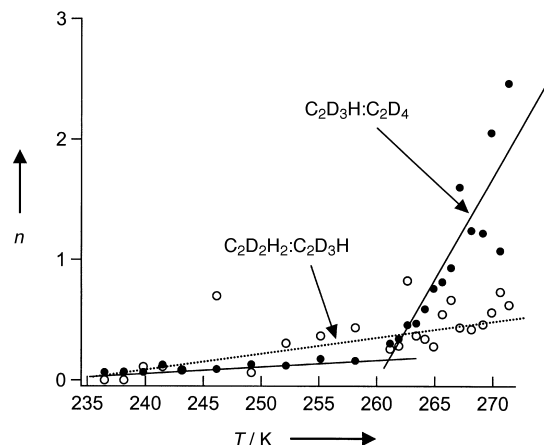
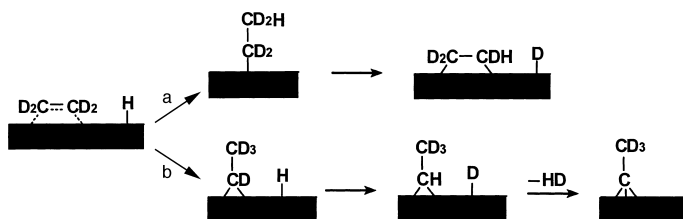


Figure 3. Relative amounts of  $C_2D_4$ ,  $C_2D_3H$ , and  $C_2D_2H_2$  on Pt(111) in the H/D exchange process;  $n$  = relative amount. The experimental conditions are the same as those in Figure 2.

Based on our observations and the information available in the literature, we propose the mechanism for the H/D exchange reaction of ethylene on Pt(111) as summarized in Scheme 2. At temperatures lower than 260 K, the reaction proceeds via ethyl intermediate (reaction a). When the surface temperature reaches 265 K, ethylidene species is formed and  $C_2D_3H$  is produced alternatively by  $\alpha$ -hydrogen exchange (reaction b). Ethylidene finally decomposes to ethynylidyne at higher temperatures.



Scheme 2. Proposed reaction mechanisms for the H/D exchange reaction of ethylene on Pt(111); a  $\leq 265$  K; b  $\geq 265$  K

It is generally accepted that the ethyl species is the common intermediate for the H/D exchange reaction and hydrogenation of ethylene on Pt(111).<sup>[4, 6, 12]</sup> The ethyl species is believed to be in fast equilibrium with ethylene on the surface and the equilibrium is shifted towards the ethylene side.

The presence of ethylidene in the temperature range of 260–290 K during ethylene reaction on Pt(111) has been reported by several groups.<sup>[10, 13, 14]</sup> We investigated the presence of ethylidene on the surface using the  $Cs^+$  RIS technique. Because ethylidene and ethylene have the same mass, they cannot be identified by simple mass analysis of

scattered  $Cs^+$ -molecule ions. To resolve this problem, we investigated the change of the  $[CsC_2H_4]^+$  ion signal as a function of  $Cs^+$ -ion impact energy in our separate set of experiments. We have found that the yield of the  $[CsC_2H_4]^+$  ion at 280 K requires a  $Cs^+$ -ion impact energy higher than that at 220 K, which implies that the  $C_2H_4$  species is more strongly bound at 280 K than at 220 K. The strongly bound  $C_2H_4$  species was assigned as ethylidene moiety.<sup>[15]</sup>

In conclusion, we have directly identified that H/D substituted ethylene molecules exist on the Pt(111) surface during the reaction between  $C_2D_4$  and H. The relative populations for  $C_2D_{4-x}H_x$  ( $x = 0-4$ ) species were determined and their variation with temperature was measured in real time. Based on quantitative analysis of  $C_2D_{4-x}H_x$  species on the surface, we proposed two different channels for the H/D exchange reaction on the surface. The capability of the  $Cs^+$  RIS technique is ideally suited for the kinetic study of surface reactions especially when similar molecules are present on the surface.

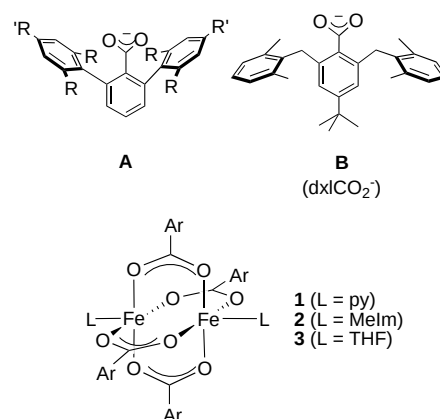
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# Unusual Peroxo Intermediates in the Reaction of Dioxygen with Carboxylate-Bridged Diiron(II,II) Paddlewheel Complexes\*\*

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The class of nonheme diiron enzymes comprising methane monooxygenase (MMOH), ribonucleotide reductase (RNR),  $\Delta^9$  stearoyl-acyl carrier protein desaturase ( $\Delta^9$ D), and others<sup>[1,2]</sup> performs a diverse array of important biological reactions that involve the binding and activation of dioxygen at a diferrous site ligated by four carboxylate and two histidine imidazole groups. Several intermediates in these systems have been identified, including (peroxo)diiron(II,II) species<sup>[3]</sup> that evolve into substrate-oxidizing diiron(II,IV) ("X" in RNR)<sup>[4]</sup> or diiron(IV,IV) ("Q" in MMO) units.<sup>[5]</sup> Investigations of synthetic models of these intermediates have provided key chemical insights.<sup>[2,6]</sup> Notwithstanding these successes, further efforts with models that incorporate the biological 4-carboxylate/2-N-donor ligand set are required to address key unresolved mechanistic issues, such as the factors responsible for the divergent reactivity of the structurally similar active sites in the various enzymes. We<sup>[7]</sup> and others<sup>[8]</sup> have begun to apply a new strategy toward this end involving the use of sterically hindered carboxylate ligands such as **A** (Scheme 1) to control structure and coordination number and to mimic the hydrophobic protein environment in diiron complexes. Herein we report a new member of this ligand class ( $\text{dxlCO}_2^-$ , **B**) that has less bulky *ortho*-dibenzyl substituents for the synthesis of a series of diiron(II,II) complexes with the common "paddlewheel" motif. Although structurally similar to other reported diiron(II,II) compounds of this type,<sup>[8b,c,9]</sup> the complexes supported by **B** react differ-



Scheme 1. Hindered carboxylate ligands (**A** and **B**) and diiron(II,II) paddlewheel complexes (**1–3**).

ently with dioxygen at low temperature to cleanly generate stable  $\text{O}_2$  adducts with unusual characteristics.

Reaction of the aryl bromide  $\text{dxlBr}$ <sup>[10]</sup> with 2.1 equivalents of *t*BuLi in  $\text{Et}_2\text{O}$  at  $-80^\circ\text{C}$  followed by addition of  $\text{CO}_2(\text{g})$  and acidification yielded the carboxylic acid  $\text{dxlCO}_2\text{H}$  in excellent yield (96 %; see Supporting Information for details). Admixture of  $(\text{Et}_3\text{NH})(\text{dxlCO}_2^-)$  (2 equiv),  $\text{Fe}(\text{OTf})_2 \cdot 2\text{MeCN}$  (1 equiv), and ligand **L** (1 equiv, **L** = pyridine (py) or 1-methylimidazole (MeIm)) in  $\text{CH}_2\text{Cl}_2$  yielded the respective complexes **1** (**L** = py) and **2** (**L** = MeIm) that were recrystallized from  $\text{CH}_2\text{Cl}_2$ /pentane (Scheme 1). In the absence of added **L**, recrystallization of the reaction product from THF/pentane yielded **3** (**L** = THF), which could be converted to **1** or **2** by adding the appropriate N-donor ligand. The formulations of **1–3** as paddlewheel complexes were confirmed by X-ray crystallography.<sup>[11]</sup>

Exposure of colorless or pale yellow solutions of **1–3** in scrupulously<sup>[12]</sup> dry  $\text{CH}_2\text{Cl}_2$  or toluene at  $-80^\circ\text{C}$  to  $\text{O}_2$  yielded deep red-brown intermediates, which are characterized by a broad absorption feature with  $\lambda_{\text{max}}$  500–550 nm and  $\epsilon \sim 1000\text{--}1200\text{ M}^{-1}\text{cm}^{-1}$ . Although stable at  $-80^\circ\text{C}$  for days, warming induced decomposition as indicated by conversion to light green solutions. Stopped-flow kinetics studies of the oxygenation reactions ( $\text{CH}_2\text{Cl}_2$ ,  $-80^\circ\text{C}$  to  $-20^\circ\text{C}$ )<sup>[13]</sup> showed that the rate of intermediate formation is described by  $d[\text{intermediate}]/dt = k[\text{diiron(II,II) complex}][\text{O}_2]$ , with second-order rate constants  $k(-40^\circ\text{C}) = 210\text{--}320\text{ M}^{-1}\text{s}^{-1}$ . Small  $\Delta H^\ddagger$  and large negative  $\Delta S^\ddagger$  values typical of associative processes were observed (Table 1) that are similar to those previously reported for other associative oxygen-binding reactions of diiron(II,II) complexes.<sup>[14]</sup> The activation parameters are closely correlated, and the Arrhenius plots cross at an isokinetic temperature of  $-57^\circ\text{C}$ , indicating similar rate-limiting steps for the series of complexes.

Table 1. Activation parameters for the oxygenations of complexes **1–3**.

| Complex  | $\Delta H^\ddagger$ [kJ mol <sup>-1</sup> ] | $\Delta S^\ddagger$ [J K <sup>-1</sup> mol <sup>-1</sup> ] |
|----------|---------------------------------------------|------------------------------------------------------------|
| <b>1</b> | $7 \pm 2$                                   | $-178 \pm 20$                                              |
| <b>2</b> | $10 \pm 2$                                  | $-153 \pm 20$                                              |
| <b>3</b> | $14 \pm 2$                                  | $-135 \pm 20$                                              |

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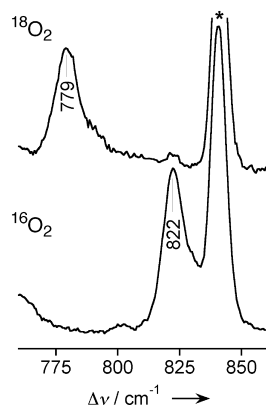


Figure 1. Resonance Raman spectra of the intermediates derived from the oxygenation of **1** with  $^{16}\text{O}_2$  and  $^{18}\text{O}_2$  ( $\lambda_{\text{ex}} = 615$  nm,  $[\text{D}_8]\text{toluene}$  solutions, 77 K). The asterisk indicates a solvent band.

Spectroscopic studies of the intermediate derived from **1** ( $\text{L} = \text{py}$ ) have provided key insights into its nature. Resonance Raman spectra were acquired on frozen  $[\text{D}_8]\text{toluene}$  solutions at 77 K using  $\lambda_{\text{ex}} = 615$  nm with  $^{16}\text{O}_2$  and  $^{18}\text{O}_2$  (Figure 1). We attribute the feature centered at  $822\text{ cm}^{-1}$  that shifts by  $43\text{ cm}^{-1}$  upon use of  $^{18}\text{O}_2$  to a peroxo O–O stretch.<sup>[15]</sup> The  $\nu(\text{O}–\text{O})$  value is notably lower than those associated with most<sup>[16]</sup> diiron complexes with  $\mu$ -1,2-peroxo ligation ( $848$ – $910\text{ cm}^{-1}$ ),<sup>[17, 18]</sup> but compares more favorably to those identified in nonheme monoiron compounds with  $\eta^2\text{-O}_2$  coordination (range  $816$ – $827\text{ cm}^{-1}$ ).<sup>[17a, 19, 20]</sup>

The Mössbauer spectrum at 4.2 K of diferrous **1** (not shown) consists of one quadrupole doublet with  $\Delta E_Q = 3.23(3)$  and  $\delta = 1.14(2)\text{ mms}^{-1}$ . The spectrum of the intermediate derived from **1** in frozen toluene solution at 4.2 K (Figure 2a) exhibits two doublets in a 1:1 ratio, with  $\Delta E_Q(1) = 1.27(3)$ ,  $\delta(1) = 0.65(2)\text{ mms}^{-1}$  and  $\Delta E_Q(2) = 0.71(2)$ ,  $\delta(2) = 0.52(2)\text{ mms}^{-1}$ . While the value of  $\delta(2)$  is characteristic of

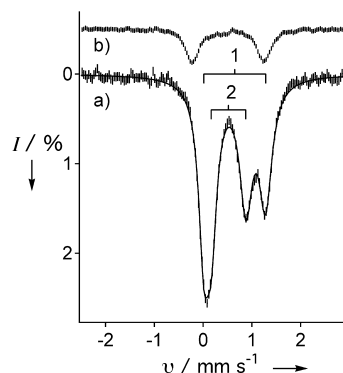
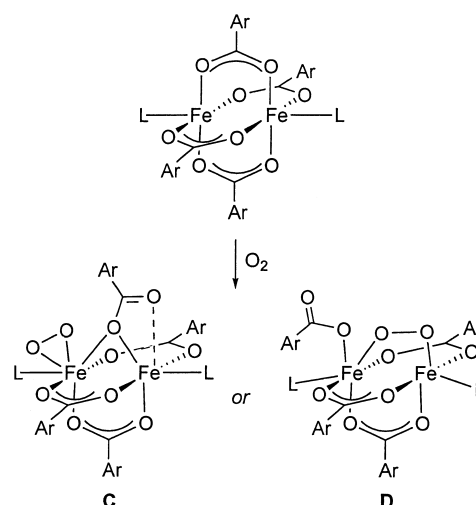


Figure 2. Mössbauer spectra recorded at 4.2 K of toluene solutions of (a) the intermediate derived from the oxygenation of **1** minus the spectrum of its decay product (b), comprising  $\sim 10\%$  of the sample. See text for the parameters associated with the doublets labeled 1 and 2.

high-spin ferric complexes with N/O coordination,<sup>[21]</sup> the value for  $\delta(1)$  is atypical. Such an isomer shift has been associated with the iron centers of peroxo intermediates of nonheme diiron enzymes,<sup>[3a, 22]</sup> some  $(\mu$ ,-1,2-peroxo)diferric complexes,<sup>[23]</sup> and  $(\eta^2\text{-peroxo})\text{monoiron(III)}$  complexes.<sup>[24]</sup> The observation of two doublets allows two interpretations: 1) Doublet 1 reflects a symmetric peroxo complex with equivalent iron sites and doublet 2 represents a symmetric diferric complex, or 2) the spectrum is derived from one complex with distinct ferric sites. We favor the latter interpretation because the two doublets occur in a 1:1 ratio (in multiple samples comprising different mixtures of the intermediate and its decay product) and their parameters differ from those of a

diferric product of the intermediate's decay (Figure 2b). A diiron(III,III)–peroxo intermediate with similarly distinct iron sites ( $\delta(1)\ 0.63\text{ mms}^{-1}$ ;  $\delta(2)\ 0.48\text{ mms}^{-1}$ ) also has been reported, but other properties of this species differ from those of the intermediate derived from **1**.<sup>[23c]</sup> Finally, Mössbauer spectra recorded at 4.2 K in strong applied magnetic fields (8.0 T) showed that both doublets belong to a diamagnetic site, and data obtained at 20, 40 and 80 K showed that  $J \approx 30(5)\text{ cm}^{-1}$  ( $J\text{S}_1 \cdot \text{S}_2$ ). This value is lower than those reported previously for  $\text{Fe}_2(\mu$ -1,2- $\text{O}_2$ ) compounds ( $66$ – $200\text{ cm}^{-1}$ ).<sup>[16, 25]</sup> Consistent with the finding of a diamagnetic ground state, solutions of the intermediates derived from **1** and **2** are EPR silent (X-band, 4 K).

Several novel structures for the intermediate are consistent with the combined spectroscopic data (Scheme 2). The low  $\nu(\text{O}–\text{O})$  value ( $822\text{ cm}^{-1}$ ) and the relatively weak antiferromagnetic coupling between the ferric centers ( $J \approx 30\text{ cm}^{-1}$ ) diverge from values for all  $\text{Fe}_2(\mu$ -1,2- $\text{O}_2$ ) complexes reported



Scheme 2. Postulated structures for the intermediate derived from the oxygenation of the paddlewheel complexes.

to date.<sup>[17, 18, 25]</sup> To explain these data, as well as the inequivalent  $\text{Fe}^{\text{III}}$  sites indicated by Mössbauer spectroscopy, we suggest a  $\text{Fe}^{\text{III}}\text{-X-Fe}^{\text{III}}(\eta^2\text{-O}_2)$  unit as one possible formulation (**C**), with the peroxo group bound to the  $\text{Fe}^{\text{III}}$  center with  $\delta = 0.65\text{ mms}^{-1}$  (ligand L may or may not be bound). The observed  $J \approx 30(5)\text{ cm}^{-1}$  is consistent with magnetic superexchange via a monodentate carboxylate O-atom bridge, as similar values are well-established for diiron sites bridged by  $-\text{OR}$  ( $\text{R} = \text{H}$ , alkyl, aryl) groups.<sup>[26]</sup> The indicated carboxylate coordination is that derived from a “least motion pathway” from the paddlewheel starting material that would provide a single O-atom bridge through one carboxylate shift,<sup>[27]</sup> but other related carboxylate dispositions may be envisaged that also would be consistent with the experimental data. A peroxo-bridged formulation (e.g. **D**) like those proposed previously for another system<sup>[23c]</sup> cannot be excluded. However, such a structure must be sufficiently asymmetric to rationalize the two doublets in the Mössbauer spectrum and, furthermore, would have to give rise to unusually low  $\nu(\text{O}–\text{O})$  and low  $J$  values.

Whatever the detailed structure of the intermediate, it is important to note that the generation of an unsymmetric diiron–peroxo species in the oxygenations of diiron(II,II) complexes supported by  $\text{dxlCO}_2^-$  contrasts with the reactivity of diiron(II,II) complexes supported by more sterically hindered carboxylates **A** (Scheme 1). For  $\text{R}=\text{R}'=\text{Me}$ , a symmetric diiron–peroxo species is formed,<sup>[7a]</sup> while for  $\text{R}'=\text{Me}$  and  $\text{R}=\text{H}$ , a mixture of  $\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}$  and  $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$  species is generated,<sup>[8b,c]</sup> presumably via an as yet unobserved peroxo intermediate. The entirely different  $\text{O}_2$  reactivity of diiron(II,II) complexes that have closely similar paddlewheel core topologies yet different carboxylate substituents underscores the importance of slight variations in steric bulk and flexibility of supporting ligands in diiron complex chemistry. Moreover, the findings suggest that similar perturbations beyond the primary metal coordination sphere should be considered in efforts to rationalize the divergent dioxygen activation pathways followed by the structurally similar active sites in the class of nonheme diiron enzymes.

### Experimental Section

$(\text{py})_2\text{Fe}_2(\mu\text{-dxlCO}_2)_4$  (**1**): A solution of  $\text{dxlCO}_2\text{H}$  (1.00 g, 2.4 mmol) and  $\text{Et}_3\text{N}$  (336  $\mu\text{L}$ , 2.41 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL) was added to a solution of  $\text{Fe}(\text{OTf})_2 \cdot 2\text{MeCN}$  (0.53 g, 1.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL), all under an  $\text{N}_2$  atmosphere. Pyridine (py, 98  $\mu\text{L}$ ) was added to this mixture and the solution was allowed to stir for 14 h. The solution was then allowed to stand at room temperature for 24 h and crystals formed (note: seeding hastens this process). The crystallization mixture was then cooled to  $-20^\circ\text{C}$  for 14 h to afford more crystals. The crystals were harvested and pentane (15 mL) was added to the mother liquor followed by cooling at  $-20^\circ\text{C}$  to afford a second crop (total yield 0.89 g, 77%). UV/Vis ( $\text{CH}_2\text{Cl}_2$ ,  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ,  $\text{M}^{-1}\text{cm}^{-1}$ ): 367 (1430); FTIR (KBr pellet,  $\text{cm}^{-1}$ ):  $\tilde{\nu}=3068$  (m), 3022 (m), 2965 (s), 2868 (m), 1603 (vs), 1470 (s), 1449 (s), 1398 (s), 1280 (w), 1224 (w), 1173 (m), 1101 (m), 1039 (m), 963 (w), 886 (w), 768 (s), 701 (m), 584 (m); elemental analysis calcd for  $\text{C}_{126}\text{H}_{142}\text{N}_2\text{O}_8\text{Fe}_2$ : C 78.65, H 7.44; found: C 78.07, H 7.22. Data for compounds **2** and **3** are listed in the Supporting Information.

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 [11] Crystal data for **1**:  $\text{C}_{126}\text{H}_{142}\text{Fe}_2\text{N}_2\text{O}_8$ ,  $M_r=1924.12$ , yellow blocks of dimensions  $0.22 \times 0.08 \times 0.07$  mm, monoclinic, space group  $P2_1/c$ ,  $a=11.1180(8)$ ,  $b=26.635$  (2),  $c=19.277(2)$  Å,  $\beta=92.819(1)^\circ$ ,  $V=5701.4(7)$  Å<sup>3</sup>,  $Z=2$ ,  $\rho_{\text{calcd}}=1.121$  mgm<sup>-3</sup>. The data were collected at 173(2) K on a Bruker SMART diffractometer equipped with a CCD detector ( $2\theta=55^\circ$ ) using  $\text{MoK}_\alpha$  radiation ( $\lambda=0.71073$ ). A total of 40177 reflections were measured, of which 12926 were unique. The structure was solved by the direct methods program SHELXS and refined by full-matrix least-squares on  $F^2$  and Fourier techniques using SHELXTL-97 (Bruker-AXS, Inc., Madison, WI). Absorption corrections were applied with the program SADABS. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned idealized positions and refined as riding atoms with individual (or group if appropriate) isotropic displacement parameters. Final residuals were  $R1=0.0544$  and  $wR2=0.1459$  for 6637 observed reflections having  $I>2(I)$  and 634 variable parameters. 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-169142–169144 (**1–3**). 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).  
 [12] The presence of trace water in the solutions of **1–3** prior to oxygenation inhibits formation of the intermediates.  
 [13] Reactions were studied under conditions of excess  $\text{O}_2$  (pseudo-first order, [diiron complex]=0.15–0.3 mM,  $[\text{O}_2]=1.2\text{–}3$  mM) and equal  $\text{O}_2$  (second-order, [diiron complex]=[ $\text{O}_2$ ]=1.5 mM), with monitoring at 550 nm. The kinetic measurements were performed by using a cryogenic stopped-flow instrument (Hi-Tech Scientific SF-43, Salisbury, Wiltshire, UK) equipped with stainless steel plumbing, a 1.00 cm stainless steel mixing cell with sapphire windows, and an anaerobic gas-flushing kit. The mixing cell was maintained to  $\pm 0.1$  K, and the mixing time was 2–3 ms. Representative kinetic traces and Eyring plots are provided in the Supporting Information.  
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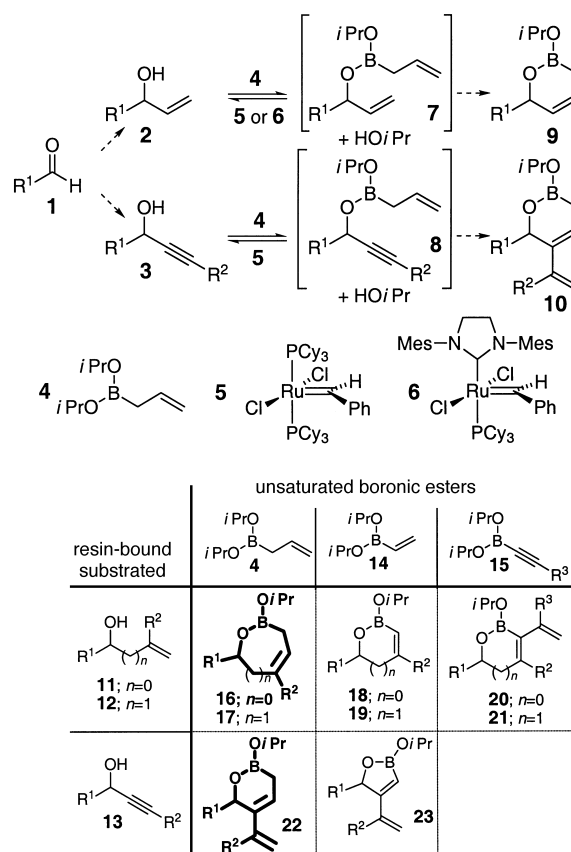
## A Boronic Ester Annulation Strategy for Diversity-Oriented Organic Synthesis\*\*

Glenn C. Micalizio and Stuart L. Schreiber\*

Diversity-oriented organic synthesis<sup>[1]</sup> can be used to prepare complex and diverse small molecules efficiently. By coupling this approach to phenotypic and proteomic screening, a systematic means to explore biology may be realized.<sup>[2, 3]</sup> Although efficient pathways leading to families of structurally complex small molecules are being reported with increasing frequency,<sup>[4]</sup> pathways leading to structurally diverse products, with many different skeletal arrays, are rare. The primary reason for this gap in our planning capabilities is that efficient and effective “branching” pathways remain elusive. Such pathways require the identification of a substrate or class of substrates that can be differentially manipulated, in single transformations, to afford products containing distinct skeletal arrays of connecting atoms. Here we report new annulation reactions of unsaturated boronic esters with allylic and propargylic alcohols, as well as oxidation and cycloaddition reactions of the resulting cyclic organoboronic esters,

which are well-suited for diversity-generating, branching pathways.<sup>[5, 6]</sup>

We anticipated that the transesterification of unsaturated boronic esters (**4**) with allylic (**2**) or propargylic alcohols (**3**) would transiently provide mixed organoboronic esters (**7** or **8**) (Scheme 1),<sup>[7]</sup> which could be trapped using ring-closing metathesis<sup>[8]</sup> to afford cyclic boronic esters (**9** and **10**).<sup>[9]</sup> The pairing of unsaturated carbinols (**11**, **12**, or **13**) and unsaturated boronic esters (**4**, **14**, or **15**) was envisioned to provide a diverse family of boron-containing heterocycles (**16–23**) whose unsaturation would facilitate subsequent functionalization reactions.



Scheme 1. Boronic ester annulation and conceptual matrix of resulting boron-containing heterocycles; bolded structures illustrate the skeletal types realized in this study. Mes = mesityl = 2,4,6-trimethylphenyl.

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

The annulation was tested with the triisopropylsilyl ether containing propargylic (**24**) and allylic alcohols (**25** and **26**) as a model for the alkylsilyl-tethered, high-capacity solid support<sup>[10]</sup> used in a one-bead, one-stock solution technology platform.<sup>[11]</sup> Treatment of propargylic alcohol **24** with allylboronic ester **4**<sup>[12]</sup> and Grubbs' catalyst (**5**) in CH<sub>2</sub>Cl<sub>2</sub> at reflux afforded the cyclic dienyl boronic acid **31** in 91% yield (Table 1, entry 1). The allylic alcohol **25** was transformed under similar reaction conditions to the cyclic allylboronic acid **32** (84% yield), whereas the substituted allylic alcohol **26** afforded **33**, which, after oxidation, gave the stereodefined trisubstituted olefin **38** in 56% overall yield (Table 1, entries 2 and 3). The annulation-oxidation sequence was similarly



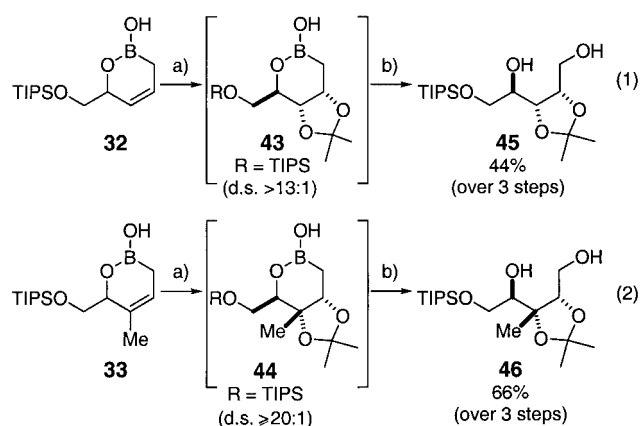
Table 1. Allylboronic ester annulation.

| Entry | Substrate | Annulation product (yield) | Oxidation product |
|-------|-----------|----------------------------|-------------------|
| 1     |           |                            |                   |
| 2     |           |                            |                   |
| 3     |           |                            |                   |
| 4     |           |                            |                   |
| 5     |           |                            |                   |
| 6     |           |                            |                   |
| 7     |           |                            |                   |

Annulation conditions: [a] **4** (3 equiv), **5** (20 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux; [b] **4** (3 equiv), **5** (10 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux; [c] **4** (2 equiv), **6** (12 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux; [d] **4** (2 equiv), **6** (7 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux; [e] **4** (2 equiv), **5** (8–9 mol %), CH<sub>2</sub>Cl<sub>2</sub>, reflux. Oxidation conditions: H<sub>2</sub>O<sub>2</sub>, NaOH (1N), THF, RT.

effective with the doubly activated allylic alcohol **27** to afford the trisubstituted *Z* olefin **39** in 60% yield (Table 1, entry 4). Aromatic- as well as alkyl-substituted propargylic alcohols (**28–30**) were excellent substrates for the annulation and provided the cyclic dienyl boronates **35–37** in 78–92% yield (Table 1, entries 5–7). Oxidation of **35–37** then gave the stereodefined trisubstituted dienyl carbinols **40–42** (59–74% yield).

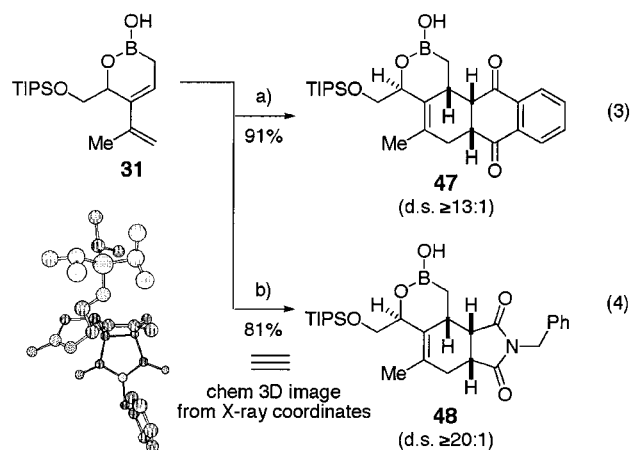
The cyclic allylboronic acids (**32** and **33**) are excellent substrates for diastereoselective dihydroxylation.<sup>[13]</sup> A three-step reaction sequence<sup>[14]</sup> converted the cyclic boronic acid **32** into the differentially functionalized xylitol derivative **45** with > 13:1 diastereoselectivity [Scheme 2, Eq. (1)]. Similarly, the trisubstituted allylboronic acid **33** was converted into the



Scheme 2. Chemoselective and diastereoselective oxidation reactions of cyclic allylboronic acids. a) OsO<sub>4</sub>, NMO, acetone, pH 7 buffer; then 2,2-dimethoxypropane, CH<sub>2</sub>Cl<sub>2</sub>, PPTS; b) H<sub>2</sub>O<sub>2</sub>, NaOH, THF. NMO = 4-methylmorpholine *N*-oxide, PPTS = pyridinium *p*-toluene sulfonate, TIPS = triisopropylsilyl.

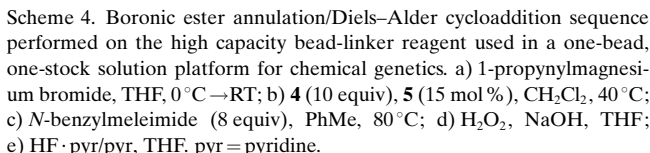
xylitol derivative **46** containing a tertiary ether with > 20:1 diastereoselectivity [Scheme 2, Eq. (2)].<sup>[15]</sup>

The boracycles can be converted efficiently into small molecules having completely different skeletons. For example, Diels–Alder cycloadditions of the dienyl boronic acid **31** provided stereoselective access to the tetracyclic and tricyclic heterocycles **47** (d.s. ≥ 13:1) and **48** (d.s. ≥ 20:1; Scheme 3). Importantly, the entire reaction sequence leading to **52** was performed efficiently on the high-capacity bead-linker reagent used in a one-bead, one-stock solution platform<sup>[10]</sup> for chemical genetics (Scheme 4).<sup>[16]</sup>



Scheme 3. Diastereoselective Diels–Alder cycloaddition reactions of cyclic dienyl boronic acids. a) 1,4-Naphthoquinone, PhMe, 70 °C; b) *N*-benzylmaleimide, PhMe, 70 °C.

This boronic ester based approach to diversity-oriented synthesis yields complex structures (namely, **35**, **40**, **46**, **47**, and **48**) containing multiple rings, stereocenters, and unsaturated units in only one to four steps. The products of this approach are strikingly dissimilar—the result of “branching” as described in the introduction. Therefore, we believe that the chemistry reported herein is promising in terms of its



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- # Microporous Supramolecular Coordination Compounds as Chemosensory Photonic Lattices\*\*

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Chemical sensing—whether for human health assessment, environmental quality monitoring, or myriad other purposes—generally entails: a) recognition and binding, adsorption, or other interaction with the molecule or ion to be sensed, and b) transduction of the recognition/binding event into an externally observable signal.<sup>[1]</sup> Coordination-based supramolecular chemistry, with its ability to generate an enormous

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variety of rigid framework assemblies featuring well-defined nanoscale cavities,<sup>[2,3]</sup> holds considerable promise for the recognition/binding phase of small-molecule sensing. With these and other chemosensory assemblies or materials, transduction is typically achieved by altering the color, luminescence intensity, redox potential, or other observable property unique to the assembly or analyte. This venerable strategy is indeed effective, but it imposes an additional sensor-design criterion that may or may not be easy to incorporate. Furthermore, the chosen transduction strategy may be difficult to generalize. We report here proof-of-concept sensing of both volatile and condensed-phase analyte molecules by using recently developed microporous supramolecular coordination compounds, in which signal transduction is achieved by a chemically universal technique based on modulated diffraction of visible light by a photonic lattice composed of the chemosensory material.

The supramolecular assembly **1** was used as a building block for the fabrication of microporous thin films.<sup>[4]</sup> The compound was obtained in a single step in quantitative yield from [ReCl(CO)<sub>5</sub>] and the difunctional porphyrin ligand by a process best described as directed assembly. Ignoring, for the moment, torsional motion around the rhenium/bridging ligand/rhenium axes, the assembly defines an open-ended nanoscale box with a cavity of approximate dimensions 18 × 18 × 18 Å. X-ray crystal structures of related compounds show that they generally pack with cavities aligned to form semi-infinite one-dimensional channels.<sup>[2a,b,5]</sup> We have shown that thin films of **1** are excellent condensed-phase molecular sieves that completely exclude a 24 Å-diameter probe mole-

micropatterned elastomeric stamp was prepared by spreading a polymer precursor over a lithographic master (an atomic force microscopy (AFM) calibration grid) and allowing the polymer to cure. The stamp was then placed on a puddle consisting of a dilute (ca. 0.5 mM) solution of **1** in chloroform, typically on a glass platform. Slow solvent evaporation in a chloroform-rich atmosphere yielded a square-perforated grid composed of **1**, which covered a few square millimeters and contained several thousand perforations. From AFM images (Figure 1), each perforation measures 9.8 × 9.8 μm with an average depth of 155 nm.

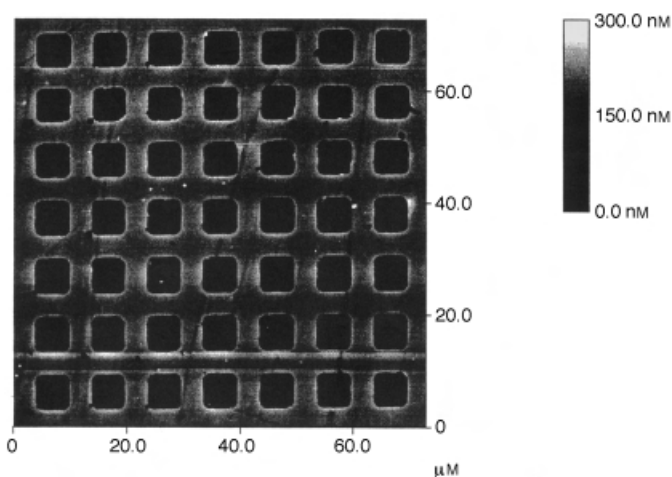
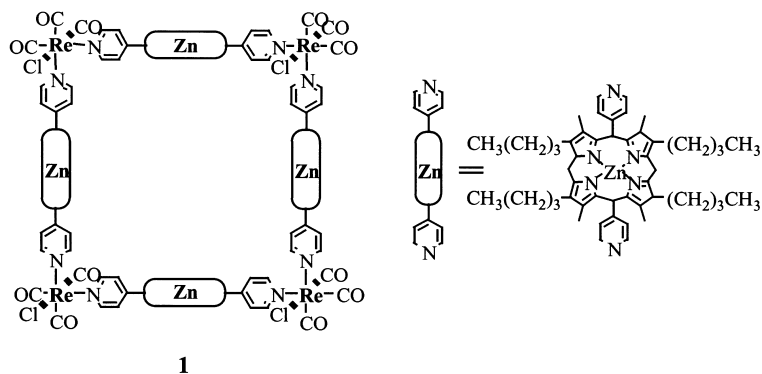


Figure 1. AFM image of a portion of a micropatterned thin film of **1** on glass. The image was obtained in tapping mode.



cule but allow 15 Å-diameter and smaller probe molecules to permeate rapidly.<sup>[4b]</sup> Important here is the absence of potentially channel blocking counterions (**1** is electrically neutral). The cavities or channels instead contain only solvent. Notably, the coordination chemistry is sufficiently robust that removal of the weakly bound solvent molecules does not collapse the cavities; instead they can be repeatedly emptied and refilled without loss of nanoscale porosity. The absence of counterions also renders the compounds completely insoluble in water, a useful property for many sensing applications.

Periodic lattice structures—the basis for optical sensing—were obtained by micromolding in capillaries, a soft lithography method developed by Whitesides et al.<sup>[6]</sup> Briefly, a

The observed lattice periodicity is appropriate for diffraction of visible light, as shown schematically in Figure 2 for coherent light of wavelength 633 nm from a He:Ne laser. The characteristic diffraction pattern is also easily observable by the naked eye on illumination with a simple laser pointer (diode laser with  $\lambda \approx 680$  nm). In the thin-film limit, the diffraction efficiency (DE) depends quadratically on the degree of refractive index contrast  $\Delta n$  between the photonic lattice and the surrounding medium<sup>[7]</sup>—in this case either air (essentially vacuum,  $n_1 = 1$ ), or water ( $n_1 = 1.33$ ). Index-matching experiments indicate a refractive index of about 1.7 for the lattice material itself, whereby the high value is due in part

to an off-resonance enhancement effect associated with the extraordinarily high extinction coefficient of the molecular square ( $\epsilon_{\text{max}} = 1.1 \times 10^6 \text{ M}^{-1} \text{ cm}^{-1}$ ).

Given an estimated void volume of greater than 50%, the lattice is best viewed as a composite of coordination compound and vacuum, with an effective refractive index  $n_2$  that is a volume-weighted average of the indices of the two components. Uptake of a molecular guest fills some of the vacuum and creates a ternary lattice/vacuum/guest composite with a refractive index that differs from the index of the simple lattice/vacuum composite. The guest-induced change in refractive index for the composite will change the degree of contrast and change DE. Figure 3 illustrates the response of a

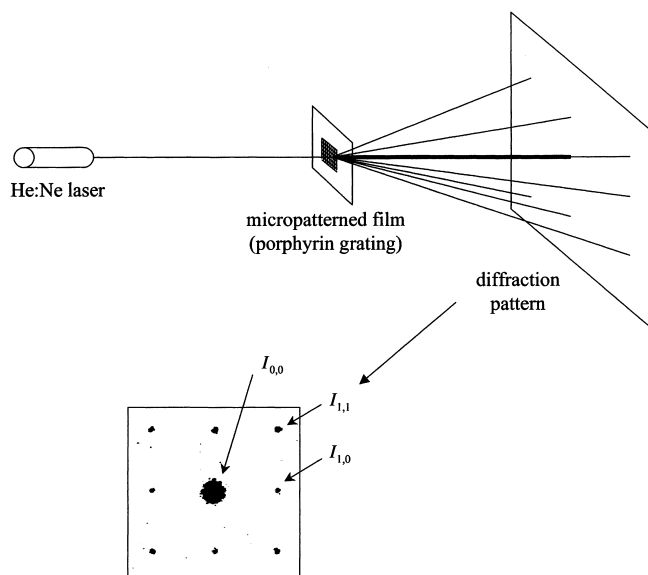


Figure 2. Schematic representation of lattice diffraction. The image shown is of a diffraction measurement made on a micropatterned thin film of **1** with a 633-nm source. The center spot, labeled  $I_{0,0}$ , corresponds to undiffracted light, whereas the points labeled  $I_{1,0}$  and  $I_{1,1}$  are one- and two-dimensional first-order diffraction spots. An expanded image (not shown) readily reveals multiple higher-order diffraction spots.

diffraction method.<sup>[9, 10]</sup> A more detailed consideration reveals that, for each of the guests, the first four guest molecules are bound more strongly than the rest. For pyridine as a guest, the first four molecules are bound about 100 times more strongly, and electronic absorption measurements indicate, as expected, that the preferential binding entails axial ligation of the four available  $\text{Zn}^{\text{II}}$  sites in the walls of the square. With the exception of that from the four strongly bound imine groups, the diffraction response is rapidly reversed upon removal of the analyte.

Since all molecules have refractive indices greater than unity, that is, higher than that of vacuum, any molecule that can be bound or absorbed by a vacancy-containing lattice will increase  $n_2$ , increase  $\Delta n (=n_2 - n_1)$ , and increase DE. In principle, therefore, the photonic lattice-diffraction technique is a chemically universal sensing technique. Most molecules also have refractive indices that exceed that of water, and this suggests sensing in aqueous phases by means of displacement of water by guests having an affinity for the nanoscale cavities. We found, for example, that the model compound, 2,4,6-tris(4-pyridyl)-1,3,5-triazine (**2**) when present in water at submillimolar concentrations, can be readily sensed in this way, where the driving forces for guest uptake by the supramolecular lattice material are diminution of hydrophobic interactions and, as noted above for vapor-phase sensing, creation of  $\text{Zn}^{\text{II}}$ /pyridine Lewis acid/Lewis base interactions (formation of weak coordinative bonds).

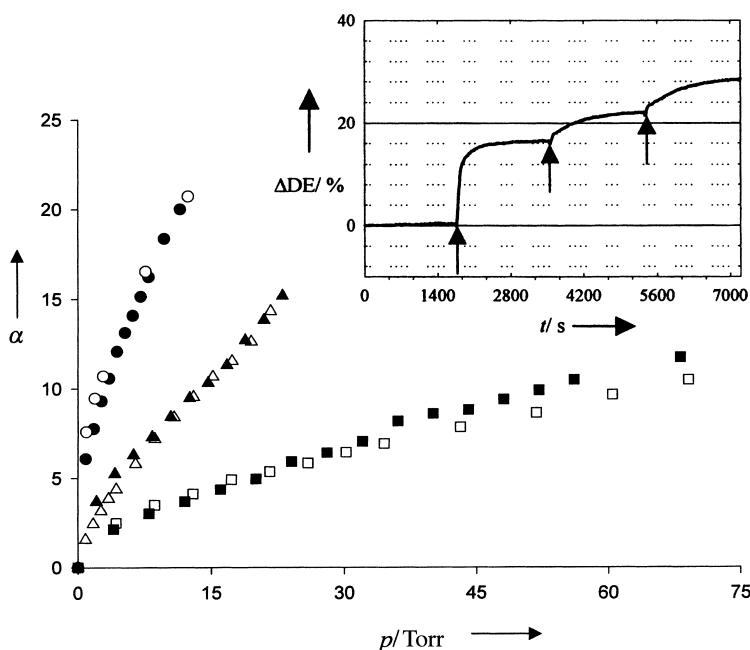
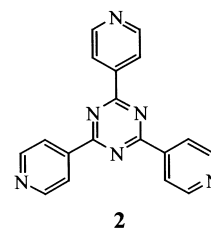
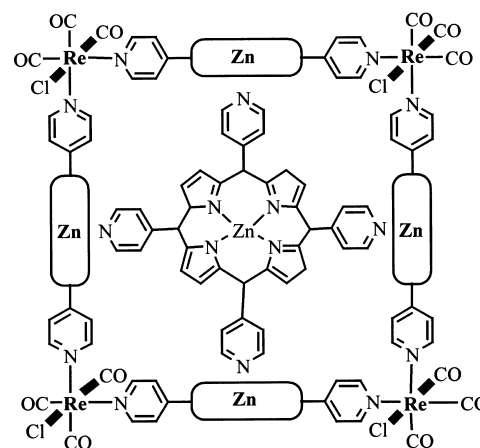


Figure 3. Thin-film sensor response expressed as number of guest molecules  $\alpha$  taken up per molecular square **1**. Filled symbols correspond to photonic lattice diffraction measurements; empty symbols correspond to QCM measurements. Key to analytes:  $\blacksquare$  = benzene,  $\blacktriangle$  = dioxane,  $\bullet$  = pyridine. Inset: Time response of thin-film sensor expressed as percentage change in initial diffraction efficiency. Arrows correspond to consecutive 7-Torr increases in the vapor pressure of pyridine.

lattice of **1** to each of three volatile organic guest molecules in a nitrogen atmosphere. Also shown are data from a series of quartz-crystal microgravimetry<sup>[8]</sup> measurements designed to assess the quantitative validity of the photonic lattice-diffraction technique. The comparison reveals nearly quantitative agreement, and also illustrates the sensitivity of the

Modification of **1** by incorporation of 5,10,15,20-tetrapyridylporphyrin<sup>[4a]</sup> to create assembly **3** eliminates the sensitivity of the lattice to the aqueous analyte, both by blocking zinc binding sites and by sterically limiting access to cavities and channels. However, the vapor-phase sensitivity to small organic compounds that can negotiate the smaller cavity entry ports is retained.



**3**

Finally, chemical tailoring of the nanoscale cavities, for example, by incorporation of receptor groups with high affinities for specific ions or molecules, opens up tremendous

possibilities for constructing highly specific photonic lattice based sensors or arrays of sensors. Using porphyrinic zinc(II) as an anchoring site, we have prepared more than 100 cavity variants,<sup>[11]</sup> several of which are chiral.<sup>[12]</sup> For example, cavity functionalization with tris(2-aminoethyl)amine renders lattices of **1** responsive to aqueous Zn<sup>II</sup> ions, whereas functionalization with 1,6-hexanedithiol enhanced the lattice response to molecular iodine by a mechanism involving formation of a charge-transfer complex. As we will show elsewhere, photonic lattice sensitivity and selectivity can also be enhanced, in many cases, by making diffraction measurements under resonance conditions, that is, at optical wavelengths coincident with lattice-based electronic transitions.

In summary, microporous molecular materials, obtained by directed coordinative assembly methods, have been used to construct chemoresponsive photonic lattices capable of functioning as chemical sensors. The photonic lattice method is, in principle, a chemically general method that requires only that the target molecule or ion contain polarizable electrons. We are currently exploring in a more general way the utility of cavity tailoring for imparting enhanced sensitivity and selectivity to microporous molecular materials. We also are evaluating the applicability of the photonic lattice methodology to problems involving other kinds of lattice materials.<sup>[13]</sup>

### Experimental Section

Compound **1** and assembly **3** were prepared as described previously.<sup>[4a,c]</sup> Compound **2** was prepared according to the literature method.<sup>[14]</sup> Micro-patterned films, prepared as described above, were stored in a vacuum desiccator overnight prior to use in sensing experiments. Films for QCM studies were prepared by passing a saturated solution of **1** in chloroform through a 0.45 µm polytetrafluoroethylene membrane (Osmotics) and then adding the solution by syringe to the gold-coated “keyhole” section of a quartz crystal (5 MHz resonator; AT-cut). Both sides of the crystal were coated. Samples were similarly desiccated prior to use. Average QCM film thicknesses (typically 100–400 nm) were determined by assuming close packing within films, redissolving films of known area in dichloromethane, and determining the total number of moles present by electronic absorption measurements. QCM measurements were performed in a sealed glass cell resistant to adsorption and absorption of volatile organic chemicals by using a home-built instrument that has been described previously.<sup>[15]</sup> Samples were introduced by syringe through a tight-fitting screw cap with a Teflon-lined septum. Diffraction measurements were performed by using the output of a He:Ne laser and recording and then ratioing the intensity of one of the first-order diffraction beams to that of the undiffracted beam. Ratioing diminishes the effects of noise and source-power variations, as well as variations in optical loss due, for example, to subtle changes in sample scattering upon analyte uptake. Intensities were recorded with photodiodes and then digitized and processed by using a module written in-house with Labview software (National Instruments, Austin, Texas). The typical resolution for  $\Delta n$  in these measurements was  $5 \times 10^{-4}$ , a value that could be significantly improved by using a mode-stabilized (power-stabilized) source and by thermostatic control of the detectors. AFM measurements were recorded with a Digital Instruments Bioscope operating in tapping mode.

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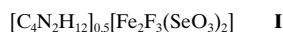
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# Three-Dimensional Organically Templated Open-Framework Transition Metal Selenites\*\*

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A large variety of open-framework metal phosphates has been synthesized and characterized in the last few years.<sup>[1]</sup> Several open-framework metal carboxylates have also been reported.<sup>[2]</sup> Besides the phosphates and the carboxylates, open-framework phosphites,<sup>[3]</sup> arsenates,<sup>[4]</sup> and germanates<sup>[5]</sup> are also known. An organically templated layered zinc selenite was described recently by Harrison et al.,<sup>[6]</sup> but no three-dimensional (3D) open-framework structure with the oxo anions of sulfur or selenium has been isolated to date. We have synthesized for the first time a 3D open-framework iron fluoroselenite templated by various organic amines. Herein we report the synthesis and structure of  $[A]^+[\text{Fe}_2\text{F}_3(\text{SeO}_3)_2]$  ( $[A] = [\text{C}_4\text{N}_2\text{H}_{12}]_{0.5}$ ,  $[\text{C}_4\text{N}_3\text{H}_{14}]_{0.5}$  or  $[\text{NH}_4]$ ) possessing an 8-ring channel. This selenite is an interesting geometrically, frustrated magnetic material by virtue of possessing near-tetrahedral  $\text{Fe}_4\text{F}_6\text{O}_{12}$  clusters, comprising equilateral triangles of Fe atoms. In addition to the Fe selenite, we have obtained a new 3D zinc selenite.

Synthesis of open-framework transition metal selenites by amine templating is difficult because of the low reduction potential of the  $\text{Se}^{\text{IV}}/\text{Se}^0$  couple, which under hydrothermal conditions may cause reduction to metallic selenium. We have therefore employed the fluoride route (addition of HF to the reaction medium) of Guth et al.,<sup>[7]</sup> as elaborated by Férey and co-workers<sup>[8]</sup> in the case of metal phosphates. The fluoride ion stabilizes the higher oxidation states of the metal and acts as a good mineralizer besides getting incorporated into the framework. Reaction of a mixture of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , HF,  $\text{SeO}_2$ , and piperazine (PIP) in water under hydrothermal conditions yields pure **I** (see Experimental Section). This inorganic



framework was obtained with diethylenetetramine (DETA), 1,3-diaminopropane (DAP), and ethylenediamine (en) as well. In the case of DAP and en, the amine decomposes to give the ammonium ion, but DETA remains intact with its two end nitrogen atoms being protonated. In the absence of fluorine in the reaction medium, only dense iron selenites were obtained.

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The 3D inorganic framework of  $[A]^+[\text{Fe}_2\text{F}_3(\text{SeO}_3)_2]$  is built up from the vertex-sharing  $\text{FeF}_3\text{O}_3$  octahedra and  $\text{SeO}_3$  pseudo-tetrahedra, and the structure can be described in terms of a unique tetrameric cluster,  $\text{Fe}_4\text{F}_6\text{O}_{12}$  (Figure 1a). Since the 3D structure obtained with all the amines was the

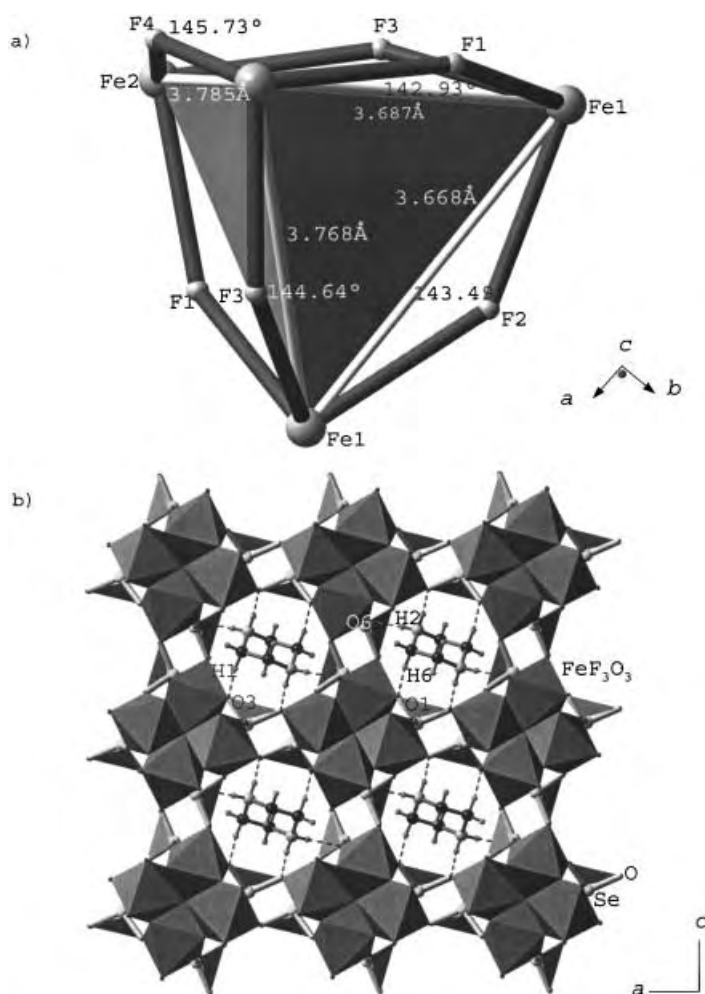


Figure 1. a) The tetrameric cluster of  $\text{Fe}_4\text{F}_6\text{O}_{12}$  in **I** formed by the corner-sharing of  $\text{FeO}_3\text{F}_3$  through six  $\text{Fe}-\mu\text{F}-\text{Fe}$  linkages. Note near perfect tetrahedron formed by connecting the Fe atoms. b) Polyhedral view of the inorganic framework of **I** along the *b* axis showing one-dimensional 8-ring channel. The amine molecules are located in the middle of the channel and interact with the framework through  $\text{N}-\text{H} \cdots \text{O}$  hydrogen bonds (dotted lines).

same, we shall only discuss **I** obtained with piperazine. The asymmetric unit of **I** contains 14 non-hydrogen atoms with two crystallographically distinct Fe and Se atoms. The Fe atoms are six-coordinate, surrounded by three oxygen atoms and three fluorine atoms. The average Fe–O bond lengths are 1.964 and 1.953 Å for Fe1 and Fe2, respectively; the corresponding Fe–F bond lengths of 1.987 and 1.982 Å are longer than in other oxyfluorinated  $\text{Fe}^{\text{III}}$  compounds.<sup>[9]</sup> The two Se atoms, each bound to three O atoms form a pyramid characteristic of the  $\text{Se}^{\text{IV}}\text{O}_3$  group, with the stereochemically active lone pair of electrons occupying the remaining tetrahedral site. The average Se–O bond lengths are 1.696 and 1.702 Å for Se1 and Se2 respectively, in agreement with

the literature values.<sup>[6]</sup> Both the Fe atoms form three Fe-F-Fe linkages and three Fe-O-Se linkages, the former being responsible for the  $\text{Fe}_4\text{F}_6\text{O}_{12}$  cluster, wherein four  $\text{FeF}_3\text{O}_4$  octahedra are corner-shared through six Fe-F-Fe linkages (Figure 1a). This connectivity between the  $\text{FeF}_3\text{O}_3$  octahedra creates four 3-rings in the cluster. The cluster, which can be considered to be the secondary building unit (SBU), is connected by Fe-O-Se linkages to form the 3D structure, possessing 4-, 5-, and 6-rings as well as an 8-ring 1D channel (with the dimensions  $5.847 \times 7.593 \text{ \AA}$ , the longest atom–atom distance, not including the van der Waal radii) along the *b* axis (Figure 1b). A section of the intercluster connectivity along the *b* axis is shown in Figure 2. The protonated PIP molecules reside in the channel and interact with the framework through strong N–H $\cdots$ O hydrogen bonding ( $d(\text{H1}\cdots\text{O3})$  1.913(8),  $d(\text{N1}\cdots\text{O3})$  2.764(8) Å,  $\theta(\text{N1-H1}\cdots\text{O3})$  156.9(7)°;  $d(\text{H2}\cdots\text{O6})$  1.841(7),  $d(\text{N1}\cdots\text{O6})$  2.740(7) Å,  $\theta(\text{N1-H2}\cdots\text{O6})$  175.2(7)°). There is evidence for C–H $\cdots$ O ( $d(\text{C}\cdots\text{O})_{\text{av}}$  3.320 Å) and C–H $\cdots$ F ( $d(\text{C}\cdots\text{F})$  3.076 Å) interactions as well.

Of the many noteworthy features in the structure of **I**, the tetrameric SBU is rather unusual. The cluster in  $[\text{A}][\text{Fe}_2\text{F}_3(\text{SeO}_3)_2]$  has a near-tetrahedral geometry with four nearly equilateral triangles, which do not share a common vertex; they are linked by Fe– $\mu_2$ –F–Fe and not capped by  $\text{SeO}_3$  pyramids (Figure 1a). The literature examples of SBUs formed by Fe–X–Fe (X = O, F, OH) linkages in open-framework phosphates or oxyfluorinated phosphates are generally constructed from a dimer, trimer, or a tetramer of edge- or corner-shared Fe– $\text{F}_x\text{O}_{6-x}$  ( $x = 0–3$ ) octahedra and capped by  $\text{PO}_4$  units; the few known iron–oxo tetranuclear clusters are also different.<sup>[10]</sup> A somewhat related tetranuclear cluster is that formed by joining of four trigonal-bipyramidal iron centers in  $[\text{enH}_2]_2[\text{Fe}_4\text{O}(\text{PO}_4)_4] \cdot \text{H}_2\text{O}$ .<sup>[11]</sup>

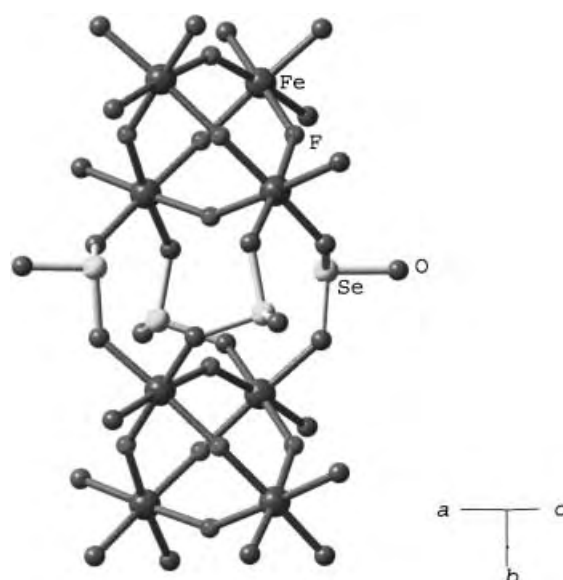


Figure 2. Section of the intercluster connectivity along the *b* axis showing the presence of 5- and 6-rings.

Variable-temperature magnetic susceptibility  $\chi$  measurements on **I** in the 2–300 K range show a continuous increase in the susceptibility with the decrease in temperature, with a sharp jump occurring around 20 K ( $T_i$ ) (Figure 3). The plot of  $1/\chi$  versus  $T$  ( $T > 150 \text{ K}$ ) is linear with a  $\mu_{\text{eff}}$  value of 6.1 characteristic of the high-spin  $\text{Fe}^{\text{III}}$  center and a  $\theta_p$  of  $-366 \text{ K}$  showing predominantly antiferromagnetic interaction. We have measured the isothermal magnetization ( $M$  versus  $H$ ) and the zero-field cooled (ZFC) susceptibility. Careful measurements showed that a small remnant field ( $\sim 1 \text{ Oe}$ ) was sufficient to force the orientation of the moments below

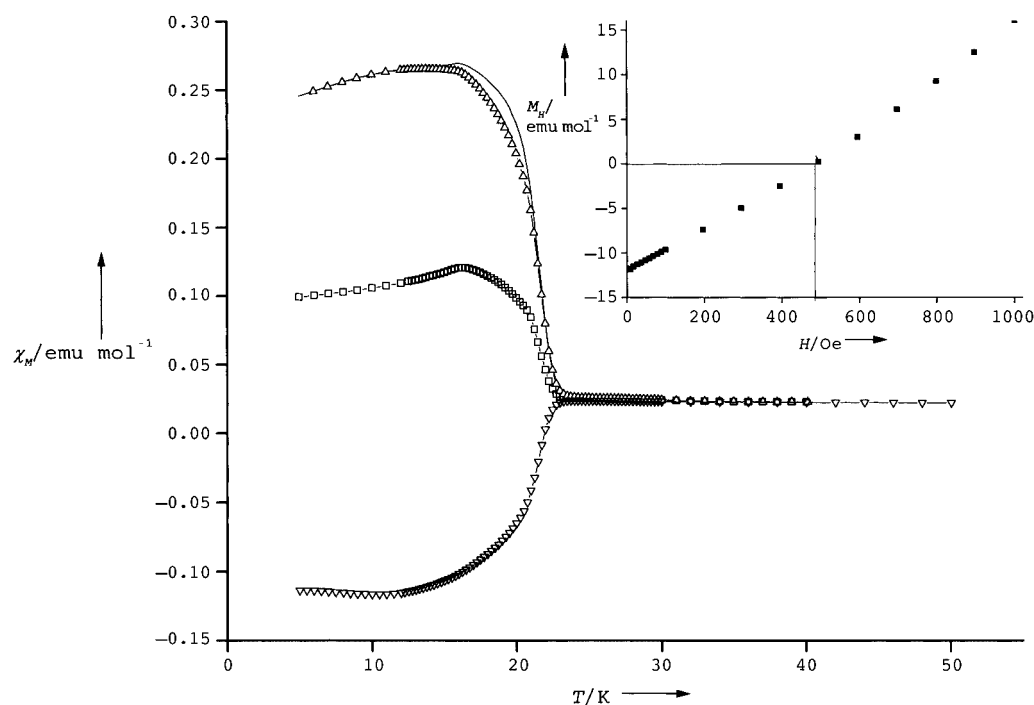
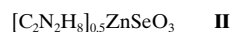


Figure 3. Temperature dependence of the magnetic susceptibility for **I** measured in the presence of a magnetic field of 100 Oe under ZFC and FC conditions. Inset: Section of the  $M$  versus  $H$  curve at 5 K with a  $-1 \text{ Oe}$  field-cooled state that demonstrates that a field as high as 500 Oe is required to make  $M$  positive; (— FC while decreasing  $T$ ,  $\Delta$  FC while warming,  $\square$  ZFC,  $\nabla$  ZFC (in the presence of a remnant field of  $\sim -1 \text{ Oe}$ )).



$T_i$ . The ZFC data, recorded after making sure that the remnant field was much smaller than 1 Oe but on the positive side of zero, reveal the divergence shown in Figure 3. We have measured the  $M$  versus  $H$  curve as well as the ZFC curve after cooling at a small remnant field of  $-1$  Oe. The ZFC curve becomes negative under these conditions as shown in Figure 3, a behavior reported earlier for  $\text{Ca}_3\text{LiRuO}_6$ <sup>[12]</sup> and for low-dimensional  $\text{AFe}^{\text{II}}\text{Fe}^{\text{III}}(\text{C}_2\text{O}_4)_3$ .<sup>[13]</sup> A field of about 500 Oe is required to make  $M$  positive in the  $M$  versus  $H$  plot (Figure 3). The  $M$  versus  $H$  curve at 5 K is practically linear and does not exhibit any spontaneous magnetization. While the magnetic behavior of **I** is clearly due to magnetic frustration, it is not due to a spin glass as corroborated by AC susceptibility measurements. The frustrated behavior may arise from the tetrahedral geometry<sup>[14]</sup> of the  $\text{Fe}^{3+}$  subnetwork of the cluster (Figure 1a) involving four near-equilateral triangles. Such tetrahedral frustrating topology has been observed earlier in the pyrochlore form of  $\text{FeF}_3$  (Pyr- $\text{FeF}_3$ ).<sup>[15, 16]</sup> The transition temperature in Pyr- $\text{FeF}_3$  is about 18 K compared to  $T_i = 23$  K in **I**. The higher  $T_i$  value in **I** indicates a relaxation of the frustrated character compared to  $\text{FeF}_3$ , due to the absence of a long-range frustration by super exchange via the  $\text{SeO}_3$  group.

We have, however, obtained an unusual open-framework 3D zinc selenite **II** by hydrothermal synthesis in the presence



of en. The polyhedral network of this selenite is built up from  $\text{ZnO}_3\text{N}$  tetrahedra and  $\text{SeO}_3$  pyramids connected to form a layer in the  $ac$  plane. The nitrogen atom in  $\text{ZnO}_3\text{N}$  tetrahedra comes from the amine (en), the other nitrogen atom of the amine coordinates to the Zn atom of the next nearest layer along the  $b$  axis to form a 3D structure. The en molecules thus act as pillars through end-to-end (Zn-N-C-C-N-Zn) connectivity and create channels along the  $a$  and  $c$  axis (Figure 4).

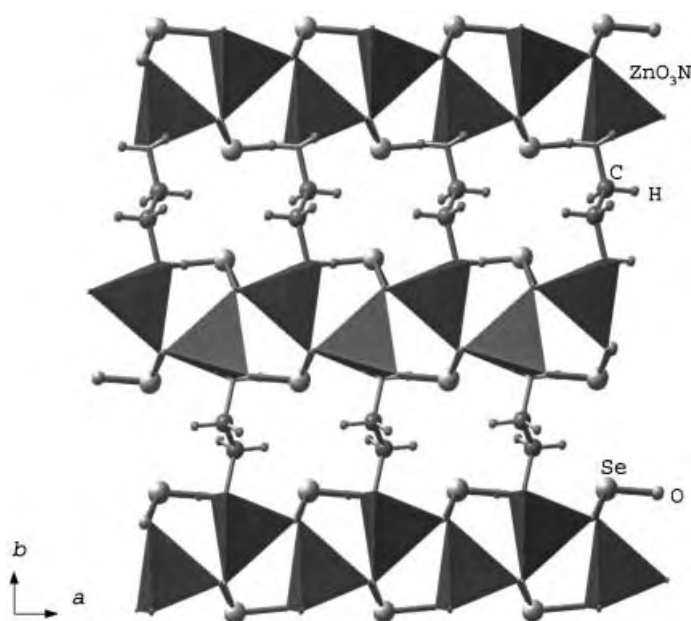


Figure 4. Structure of  $[\text{H}_2\text{N}(\text{CH}_2)_2\text{NH}_2]_{0.5} \cdot \text{ZnSeO}_3$  along the  $c$  axis, showing the zinc selenite layers pillared by the en molecule through coordinate bonds.

The structure of **II** is similar to a recently reported zinc phosphite,  $[\text{C}_2\text{N}_2\text{H}_8]_{0.5}\text{Zn}(\text{HPO}_3)_3$ , in which there are two such completely independent interpenetrating networks.<sup>[3b]</sup>

## Experimental Section

**I:**  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (0.8153 g) was dissolved in water (5.4 mL) in a teflon beaker. To this solution HF (0.43 mL) was added with stirring followed by  $\text{SeO}_2$  (0.6692 g). Finally, PIP (0.2598 g) was added to this mixture and stirring continued for another 30 min to obtain a homogeneous gel. The resulting gel with a molar ratio  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O} : 4\text{HF} : 2\text{SeO}_2 : \text{PIP} : 100\text{H}_2\text{O}$  was transferred into a 23 mL PTFE-lined stainless steel autoclave and heated at  $150^\circ\text{C}$  for 5 days. The pH of the starting reaction mixture was 2, and there was little change in pH after completion of the reaction. Rod-shaped faint brown crystals (yield 70 %) of **I** were collected, washed with deionized water, and dried under ambient conditions. Similar reactions were carried out with the amines DETA, DAP, and en.

**II:** Compound **II** was synthesized starting with the following mixture:  $\text{ZnO}$  (0.0814 g),  $\text{H}_2\text{SeO}_4$  (0.515 mL), en (0.067 mL), 36 % HCl (0.062 mL), and  $\text{H}_2\text{O}$  (3.6 mL) at  $100^\circ\text{C}$  for three days.

**Structure determination:** Single-crystal data were collected on a Siemens SMART-CCD diffractometer (graphite-monochromated  $\text{MoK}_\alpha$  radiation,  $\lambda = 0.71073 \text{ \AA}$  ( $T = 298 \text{ K}$ )). An absorption correction based on symmetry-equivalent reflections was applied using SADABS.<sup>[17]</sup> The structures were solved by direct methods using SHELXS-86<sup>[18]</sup> and difference fourier synthesis. The hydrogen atoms associated with piperazine molecules in **I** were placed geometrically and refined in the riding mode. Full-matrix least-squares structure refinement against  $|F^2|$  was carried out using the SHELXTL-PLUS<sup>[19]</sup> package of programs. The non-hydrogen atoms were refined anisotropically.

**Characterization:** The X-ray powder data for all the compounds were in excellent agreement with their simulated patterns based on single-crystal data, indicating the phase purity. The thermogravimetric analysis of **I** reveals that the selenites are thermally stable up to  $300^\circ\text{C}$ , above which there is a sharp one-step weight loss corresponding to the loss of amine molecules,  $\text{SeO}_2$ , and HF. The calcined products diffracted poorly and showed a few reflections of  $\text{Fe}_2\text{O}_3$ .

**Crystal data:**  $[\text{C}_2\text{N}_2\text{H}_{12}]_{0.5}[\text{Fe}_2\text{F}_3(\text{SeO}_3)_2]$ , **I**,  $M_r = 466.70$ , monoclinic, space group =  $C2/c$  (no. 15),  $a = 16.1683(14)$ ,  $b = 7.3973(6)$ ,  $c = 16.1275(14) \text{ \AA}$ ,  $\beta = 90.044(2)^\circ$ ,  $V = 1928.9(3) \text{ \AA}^3$ ,  $Z = 8$ ,  $\mu = 10.616 \text{ mm}^{-1}$ ,  $\rho_{\text{calcd}} = 3.14 \text{ g cm}^{-3}$ .  $[\text{C}_2\text{N}_2\text{H}_8]_{0.5}\text{ZnSeO}_3$ , **II**,  $M_r = 222.38$ , monoclinic, space group =  $P2_1/n$  (no. 14),  $a = 4.8180(7)$ ,  $b = 15.197(2)$ ,  $c = 6.4863(9) \text{ \AA}$ ,  $\beta = 91.724(2)^\circ$ ,  $V = 474.71(12) \text{ \AA}^3$ ,  $Z = 4$ ,  $\mu = 12.724 \text{ mm}^{-1}$ ,  $\rho_{\text{calcd}} = 3.112 \text{ g cm}^{-3}$ . Unique reflections: **I**, 1391 ( $R_{\text{int}} = 0.0352$ ); **II**, 686 ( $R_{\text{int}} = 0.0432$ ). Final  $R$ ,  $R_w$ : **I**, 0.03, 0.07; **II**, 0.04, 0.09. GOF: **I**, 1.07; **II**, 1.05.

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-170619 (**I**) and CCDC-170620 (**II**). 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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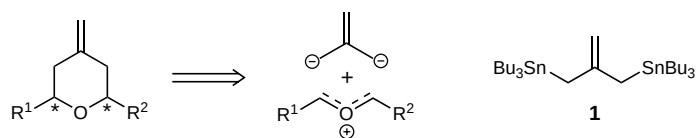
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## Sequential Catalytic Asymmetric Allylic Transfer Reaction: Enantioselective and Diastereoselective Construction of Tetrahydropyran Units\*\*

Chan-Mo Yu,\* Jae-Young Lee, Byungrun So, and Junghyun Hong

There is considerable interest in the enhancement of catalysts for Lewis acid promoted reactions so that practical and useful levels of asymmetric synthesis can be achieved.<sup>[1]</sup> Other research groups have used a ligand-accelerated strategy<sup>[2]</sup> to activate the chiral Lewis acid through the internal regulation of the chiral catalyst by a modification of the ligand, thus leading to impressive advances in carbonyl addition reactions.<sup>[3]</sup> In previous studies we demonstrated

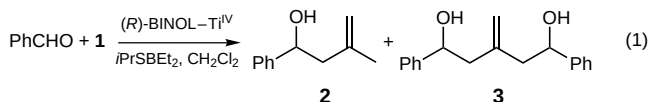
that the use of molecular synergistic reagents in catalytic asymmetric allylic transfer reactions resulted in a significant increased catalytic ability as the chiral catalyst could be regenerated expediently. Our strategy involves the use of BINOL–Ti<sup>IV</sup> complex (BINOL = 2,2'-binaphthol) as a chiral promoter along with *i*PrSBET<sub>2</sub> or *i*PrSSiMe<sub>3</sub> as an accelerating synergistic reagent. Recently, this approach provided highly catalytic versions of enantioselective allylic transfer reactions of achiral aldehydes, for example, allylation,<sup>[4]</sup> propargylation,<sup>[5]</sup> allenylation,<sup>[6]</sup> and dienylation.<sup>[7]</sup> The efficiency of this protocol in terms of enantioselectivity and catalytic ability has encouraged us to apply the extension of this method to more versatile systems, which would expand the scope and utility of allylic transfer reactions. Described herein is an extension of our strategy aimed at finding new reagents and realizing practical ways to advance new levels of asymmetric synthesis. In this study we focus on the sequential addition of a bifunctional reagent to two aldehydes to form an asymmetric tetrahydropyran system (Scheme 1). An efficient method for



Scheme 1. General protocol for the synthesis of a tetrahydropyran by means of sequential allylic transfer reactions.

this reaction would be useful in the synthesis of biologically active substances that contain a tetrahydropyran unit.<sup>[8]</sup> Several crucial points emerged from this investigation, including the development of a new catalyst and reagents for the sequential allylic transfer reaction, the introduction of highly efficient promoters for the formation of the tetrahydropyran ring, and the highly stereoselective synthesis of four different tetrahydropyran systems that contain an exocyclic double bond.

Our initial studies began with bis-stannane **1** as a dianion equivalent which was prepared from Bu<sub>3</sub>SnLi (two equivalents) and methallyl dichloride at –78 °C in THF. Initial attempts to add **1** to benzaldehyde in the presence of BINOL–Ti<sup>IV</sup> [a 2:1 mixture of BINOL and Ti(O*i*Pr)<sub>4</sub>]<sup>[9]</sup> were not successful. The reactivity was improved by introducing a synergistic reagent.<sup>[4–7]</sup> Treatment of **1** with benzaldehyde in the presence of the catalyst (10 mol %), followed by the dropwise addition of *i*PrSBET<sub>2</sub> at –20 °C for 20 h in CH<sub>2</sub>Cl<sub>2</sub> afforded undesired **3** and **2** in a combined yield of 44 % (2:1) [Eq. (1)]. The formation of alcohol **2** was attributed to a

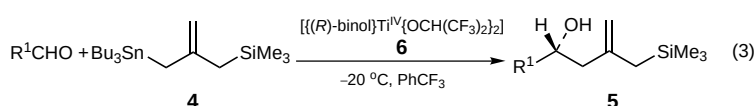
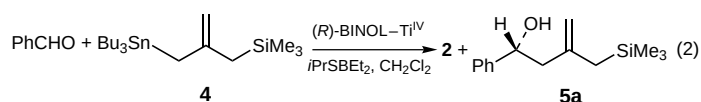


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group in **1**. As a consequence, the bifunctional reagent **4** was considered for this study [Eq. (2)].<sup>[10]</sup>

Initial experiments on the allylic transfer reaction of **4** with benzaldehyde promoted by (*R*)-BINOL–Ti<sup>IV</sup> (10 mol %) with *i*PrSBET<sub>2</sub> under similar conditions (–20 °C for 18–24 h in CH<sub>2</sub>Cl<sub>2</sub>) led to encouraging but marginal results. Although alcohol **3** was not produced during the reaction, the formation of **2** (≈15 %) and the low yield of the desired **5a** (35 to 41 %) remained to be solved.<sup>[11]</sup> After exploring various conditions, we were delighted to find that the use of alcohol-free [(*R*)-binol]Ti<sup>IV</sup>{OCH(CF<sub>3</sub>)<sub>2</sub>}<sub>2</sub> (**6**) as a chiral promoter in PhCF<sub>3</sub> always led to the best results in terms of yields and enantioselectivities. Furthermore, when **6** was used alone without any synergistic reagent, the new catalytic process was usually complete within 12 h at –20 °C.



The allylic transfer reaction was conducted by the dropwise addition of **4** in PhCF<sub>3</sub> at –20 °C to a mixture of **6** (5 mol %) and benzaldehyde in PhCF<sub>3</sub>. After 12 h at –20 °C, the mixture was quenched by the addition of saturated aqueous NaHCO<sub>3</sub>. Workup and chromatography on triethylamine-treated silica gel gave **5a** [Eq. (3)], R<sup>1</sup> = Ph, 89 %, 96 % *ee*). The reliability of the catalytic reaction was further examined with a variety of aldehydes, including aldehydes that contain a second carbonyl group (Table 1). After the conversion of **5** into **2** under acidic conditions, the absolute configuration of the predominating enantiomer of the adducts **5** was unambiguously established by comparison of their specific rotations with those of known alcohols.<sup>[4]</sup>

The second challenge in this study was the development of synthetic routes from **5** to a variety of tetrahydropyran units (Scheme 2). It was envisaged that this could be accomplished by the formation of an oxocarbenium ion from **5** or **7** with an aldehyde, with a subsequent allylic transfer reaction.<sup>[12]</sup> Nonetheless, each of the published approaches suffers from major disadvantages, such as low conversions and diastereoselectivities, and often partial isomerization of the exocyclic double bond to the endocyclic form. For example, treatment of **7a** with hydrocinnamaldehyde in the presence of TMSOTf (10 mol %; Tf = trifluoromethanesulfonyl) gave **8a** in only 24 % yield and with a 7:1 diastereoselectivity (after chromatography), together with several unidentified products. A survey of several Lewis acids, for example, TiCl<sub>4</sub>, TiCl<sub>2</sub>(OiPr)<sub>2</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, and EtAlCl<sub>2</sub>, provided no significant advantages and even gave poorer results. However, when TMSNTf<sub>2</sub><sup>[13]</sup> was employed as a promoter, the cyclization process was greatly improved in terms of yield and diastereoselectivity (**7a**, PhCH<sub>2</sub>CH<sub>2</sub>CHO, TMSNTf<sub>2</sub>

Table 1. Allylic transfer reaction from **4** to achiral aldehydes.<sup>[a]</sup>

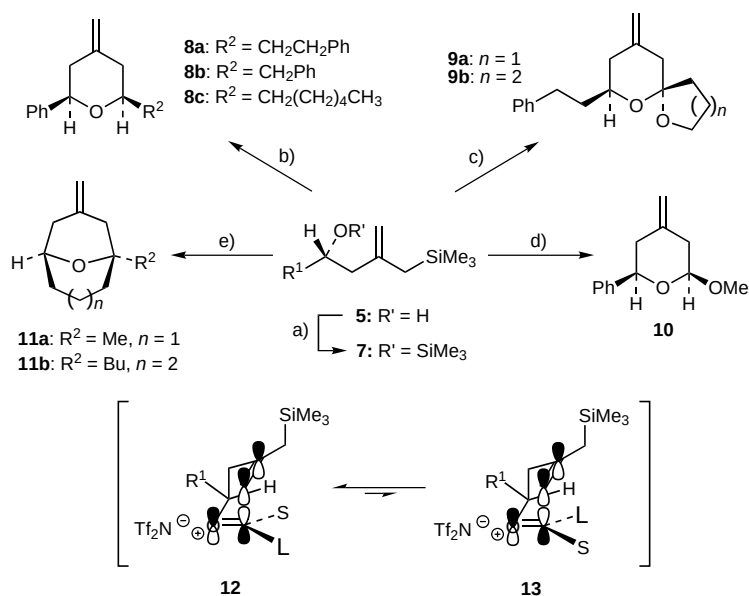
| Entry | R <sup>1</sup> CHO                                                  | <b>5</b> | <i>t</i> [h] | yield [%] <sup>[b]</sup> | <i>ee</i> [%] <sup>[c]</sup> |
|-------|---------------------------------------------------------------------|----------|--------------|--------------------------|------------------------------|
| 1     | Ph                                                                  | <b>a</b> | 12           | 89                       | 96                           |
| 2     | PhCH <sub>2</sub> CH <sub>2</sub>                                   | <b>b</b> | 12           | 74                       | 91                           |
| 3     | <i>n</i> C <sub>6</sub> H <sub>13</sub>                             | <b>c</b> | 12           | 69                       | 97                           |
| 4     | PhCH=CH                                                             | <b>d</b> | 17           | 54                       | 93                           |
| 5     | EtO <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>   | <b>e</b> | 14           | 71                       | 91                           |
| 6     | CH <sub>3</sub> COCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>   | <b>f</b> | 14           | 94                       | 90                           |
| 7     | BuCOCH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> | <b>g</b> | 16           | 87                       | 92                           |
| 8     | BuCOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>                 | <b>h</b> | 16           | 87                       | 95                           |

[a] The reaction was run at –20 °C in PhCF<sub>3</sub> with **6** (5 mol %). [b] Yields of isolated and purified products. [c] Enantiomeric excesses were determined by preparation of (+)-MTPA ester derivatives, analysis by 500-MHz <sup>1</sup>H NMR spectroscopic analysis (all entries), and by HPLC analysis on a chiral column (Chiracel OD-H, 3–5 % *i*PrOH in hexane, entries 1, 2, 4, and 6).

(10 mol %), CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1 h; **8a**, 78 %, d.r. 17:1). This Lewis acid was superior to others for the conversion of **5** or **7** into **8**, **9**, and **10** and was chosen for systematic studies (Scheme 2).<sup>[14]</sup> An improved synthetic route from alcohol **5a** (R<sup>1</sup> = Ph) gave **8a–c** in high yields and diastereoselectivities. As expected, the reaction of **7b** with 2,2-dimethoxytetrahydrofuran or pyran in the presence TMSNTf<sub>2</sub> gave **9a** and **9b**, respectively.

We were unable to detect the alternate diastereomers by 500-MHz <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analysis of the crude products, and the relative stereochemistry was confirmed by NOE experiments. In close analogy, treatment of **7a** with orthoformate under the same conditions afforded **10** in 83 % yield (d.r. 11:1).

The internal chirality transfer during the cyclization is probably a result of the geometrical preference for **12** rather



Scheme 2. Reagents and conditions: a) TMSCl, Et<sub>3</sub>N, 0 °C, 2 h, CH<sub>2</sub>Cl<sub>2</sub>, 86–97 %; b) 1. **5a**, R<sup>2</sup>CHCl(OMe), *i*PrNEt<sub>2</sub>, 0–23 °C, 12 h, CH<sub>2</sub>Cl<sub>2</sub>; 2. TMSNTf<sub>2</sub> (10 mol %), –78 °C, 1 h, CH<sub>2</sub>Cl<sub>2</sub> (**8a**, 91 %, d.r. 55:1; **8b**, 84 %, d.r. 37:1; **8c**, 87 %, d.r. 33:1); c) **7b**, 2,2-dimethoxytetrahydrofuran or -pyran, TMSNTf<sub>2</sub> (10 mol %), –78 °C, 1 h, CH<sub>2</sub>Cl<sub>2</sub> (**9a**, 81 %; **9b**, 76 %); d) **7a**, CH(OMe)<sub>3</sub>, TMSNTf<sub>2</sub> (10 mol %), –78 °C, 1 h, CH<sub>2</sub>Cl<sub>2</sub> (83 %, d.r. 11:1); e) **7f** or **7h**, Sn(OTf)<sub>2</sub> (10 mol %), Me<sub>3</sub>SiPh (2 mol %), 0–23 °C, 2 h, CH<sub>2</sub>Cl<sub>2</sub> (**11a**, 78 %; **11b**, 82 %).

than for **13**: a small pseudoaxial group minimizes allylic strain with the existing stereogenic center (Scheme 2). Thus, this allylic transfer reaction led to the formation of a *cis* tetrahydropyran with high diastereoselectivity through the stereochemical model **12**.

Having been successful in forming bridged pyran ring **11**, we tried to extend this approach to intramolecular allylic transfer reactions.<sup>[15]</sup> We were surprised that **7 f** and **7 h** did not cyclize on treatment with a variety of Lewis acids and modified substrates. After surveying numerous reaction conditions, we were gratified to find that the use of Sn(OTf)<sub>2</sub> and Me<sub>3</sub>SiSPh in the intramolecular allylic transfer reaction led to the formation of **11** as the sole product (Scheme 2, e). The use of catalytic amounts of TMSSPh was crucial, presumably as a result of the formation of a thioketal intermediate, which formed a oxocarbenium ion under mediation of the tin catalyst.

In summary, we have described herein a new synthetic strategy for the stereoselective synthesis of tetrahydropyrans with an exocyclic double bond by means of a catalytic asymmetric sequential allylic transfer reaction in a very general and efficient way, which promises to be widely applicable. We believe that the products can serve as synthetic intermediates for useful substances.

### Experimental Section

**6**:<sup>[16]</sup> (*R*)-BINOL and Ti(OiPr)<sub>4</sub> (1:1) in the presence of 4-Å molecular sieves at 45 °C in PhCF<sub>3</sub> for 2 h afforded (*R*)-BINOL–Ti<sup>IV</sup> complex. 1,1,1,3,3,3-Hexafluoro-2-propanol (2 equiv) was added to the resulting mixture. The solution was stirred at 45 °C for an additional 2 h and the volatile materials were evaporated under high vacuum (≈0.5 mmHg) in a Schlenk tube. Freshly distilled PhCF<sub>3</sub> was added.

Typical procedure (Table 1, entry 1): A flame-dried Schlenk flask that contained (*R*)-BINOL (57.3 mg, 0.2 mmol) and activated powdered 4-Å molecular sieves (1.0 g) was evacuated, carefully purged with nitrogen three times, and then charged with dry PhCF<sub>3</sub> (2 mL) followed by freshly distilled Ti(OiPr)<sub>4</sub> (freshly prepared, 0.5 M in PhCF<sub>3</sub>, 0.4 mL, 0.2 mmol). The mixture was allowed to proceed at 45 °C for 2 h. After cooling to 23 °C, 1,1,1,3,3,3-hexafluoro-2-propanol (68 mg, 0.4 mmol) was added. The resulting solution was warmed to 45 °C and heated for 2 h. The solution was cooled to 23 °C and concentrated under vacuum (≈0.5 mmHg) in a Schlenk tube. The vacuum line was equipped with a drying tube (CaSO<sub>4</sub>). Freshly distilled PhCF<sub>3</sub> (3 mL) was added, the homogeneous solution of **6** was cooled to –20 °C in a dry ice/CCl<sub>4</sub> bath, and treated with benzaldehyde (R<sup>1</sup> = Ph, 0.44 g, 4.0 mmol) in PhCF<sub>3</sub> (1 mL). The temperature was kept below –20 °C, while **4** (1.67 g, 4.0 mmol) in PhCF<sub>3</sub> (2 mL) was added dropwise through a gas-tight syringe to this mixture over 20 min along the wall of the flask by using a syringe pump. After stirring for 12 h at –20 °C, aqueous NaHCO<sub>3</sub> (5 mL) was added to the reaction mixture, which was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The molecular sieves were removed by filtration, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (≈20 mL). After the combined organic solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvents were removed under reduced pressure. Column chromatography (15% EtOAc in hexanes) afforded **5a** (R<sup>1</sup> = Ph, 0.835 g, 3.56 mmol, 89%) as a colorless liquid. *R<sub>f</sub>* = 0.26 (15:1 hexane/EtOAc); [α]<sub>D</sub><sup>20</sup> = +27.08 (c = 1.230, CHCl<sub>3</sub>); 96% *ee* determined by means of HPLC on a Daicel OD-H column [hexane/*i*PrOH 97:3; *t<sub>r</sub>*(major) = 12.4 min, *t<sub>r</sub>*(minor) = 14.2 min]; FTIR (neat):  $\tilde{\nu}$  = 3404.7 (br), 3069.9, 2953.6, 1631.7, 1250.0, 848.3 cm<sup>–1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 0.03 (s, 9H; Si(CH<sub>3</sub>)<sub>3</sub>), 1.59 (ddd, *J* = 0.92, 13.42, 13.42 Hz, 1H; (CH<sub>3</sub>)<sub>3</sub>SiCHH), 1.63 (ddd, *J* = 0.92, 13.42, 13.42 Hz, 1H; (CH<sub>3</sub>)<sub>3</sub>SiCHH), 2.29 (d, *J* = 1.83 Hz, 1H; OH), 2.34 (dd, *J* = 9.46, 13.73 Hz, 1H; HOCHCHH = C), 2.37 (ddd, *J* = 0.92, 3.97, 13.73 Hz, 1H; HOCHCHH = C), 4.75 (d, *J* = 0.91 Hz, 1H; C = CHH), 4.78 (d, *J* = 0.91 Hz, 1H; C = CHH), 4.80 (dd, *J* = 0.92, 3.97 Hz, 1H; HOCH), 7.33–7.39 (m, 5H; Ph); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = –0.95, 26.93,

49.48, 71.57, 111.49, 126.16, 127.80, 128.80, 144.44, 144.82; calcd for C<sub>14</sub>H<sub>22</sub>O<sub>2</sub>Si: C 71.73, H 9.46; found: C 71.33, H 9.55.

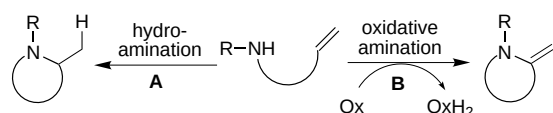
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# Efficient Intramolecular Oxidative Amination of Olefins through Direct Dioxygen-Coupled Palladium Catalysis\*\*

Shannon R. Fix, Jodie L. Brice, and Shannon S. Stahl\*

The prominence of five-membered nitrogen-containing heterocycles in natural products and biologically active molecules<sup>[1]</sup> has prompted considerable efforts toward their synthesis. Intramolecular hydroamination<sup>[2, 3]</sup> and oxidative amination<sup>[4, 5]</sup> of olefins represent powerful synthetic strategies for heterocycle formation (Scheme 1).<sup>[6]</sup> The latter is

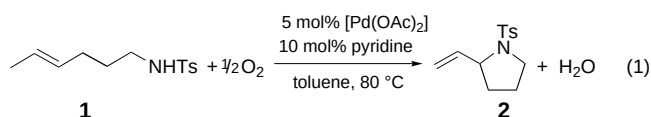


Scheme 1. Strategies for the heterocyclization of olefinic amines or amides.

particularly attractive in the context of target-<sup>[7]</sup> and diversity-oriented<sup>[8]</sup> synthesis, because the product retains the olefin functionality. Nevertheless, oxidative methods exhibit added complexity associated with redox catalysis, specifically the need for a stoichiometric oxidant, which is typically an organic or a transition metal reagent such as benzoquinone or  $\text{CuCl}_2$ .<sup>[9]</sup> Furthermore, catalytic rates ( $< 1 \text{ h}^{-1}$ ) and turnover numbers ( $\leq 10\text{--}20$ ) are significantly lower than those of hydroamination reactions, for which turnover numbers of  $\geq 300$  and frequencies of  $50 \text{ h}^{-1}$  are not uncommon.<sup>[2]</sup> We describe herein the application of a very simple and efficient catalyst system,  $[\text{Pd}(\text{OAc})_2]/\text{pyridine}$  (1:2), for the intramolecular oxidative amination of olefins to produce pyrrolidine and pyrroline heterocycles in high yields. These reactions utilize molecular oxygen as the stoichiometric oxidant, require no co-catalyst to facilitate the dioxygen-coupled catalytic turnover, and achieve unprecedented catalytic activity for such reactions.

Our recent mechanistic studies of the  $[\text{Pd}(\text{OAc})_2]/\text{O}_2/\text{DMSO}$  catalytic oxidation system<sup>[9]</sup> revealed that oxidation of reduced palladium by molecular oxygen is the turnover-limiting step of the catalytic cycle.<sup>[10]</sup> By analogy to recent aerobic oxidation reactions of alcohols,<sup>[11–13]</sup> we reasoned that pyridine or other imine donor ligands might promote palladium oxidation and thereby increase catalytic efficiency in oxidative amination reactions. Indeed, the oxidative

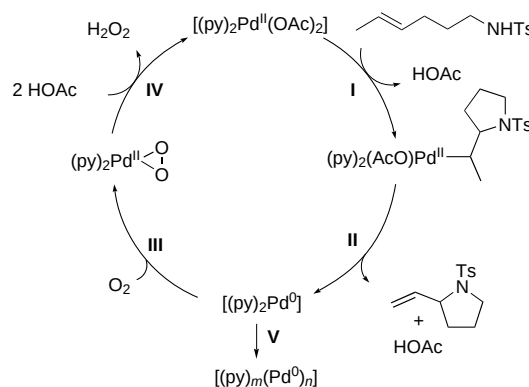
cyclization of (*E*)-4-hexenyltosylamide (**1**) worked remarkably well with a catalyst composed of  $[\text{Pd}(\text{OAc})_2]$  (5 mol %) and pyridine (10 mol %) under one atmosphere of molecular oxygen [Eq. (1)]. The pyrrolidine product **2** was obtained in high yield (87 %) within two hours.



Unlike previous aerobic oxidative amination reactions, this catalyst system operates successfully in a diverse array of solvents ( $\geq 80\%$  yield), ranging from nonpolar (toluene, xylenes, heptane, and diphenyl ether) to polar (dimethoxyethane, acetonitrile, dimethylsulfoxide, and dimethylformamide). The precise role of pyridine in more polar, potentially coordinating solvents remains to be determined.

Nonpolar solvents proved to be distinctly superior at lower catalyst loading. The use of  $[\text{Pd}(\text{OAc})_2]$  (0.2 mol %)/pyridine (0.4 mol %) in *p*-xylene resulted in turnover rates of  $70 \text{ h}^{-1}$  during the first two hours of the reaction and overall turnover numbers up to 250–300.<sup>[14]</sup> These catalyst activities far surpass those of previous oxidative amination reactions, and match or exceed the activities of most lanthanide-catalyzed hydroamination reactions. Particularly noteworthy is the lack of necessity for a co-catalyst to achieve efficient dioxygen-coupled turnover.

A possible catalytic cycle based upon experimental findings is shown in Scheme 2, although numerous details remain to be elucidated. The product arises from aminopalladation of the olefin (step I) followed by  $\beta$ -hydride elimination from the



Scheme 2. Hypothetical catalytic cycle.

alkyl palladium(II) intermediate (step II). The allylic disposition of the tosylamide in **2** arises from  $\beta$ -hydride elimination toward the methyl group, which is favored sterically and statistically over elimination that leads to the enamide product.<sup>[15]</sup> Oxygenation of palladium(0) (step III) followed by protonolysis of the peroxopalladium(II) species (step IV), as was recently demonstrated for a diimine-coordinated palladium(0) complex,<sup>[16]</sup> regenerates the active palladium(II) species.<sup>[17]</sup> Consistent with a mechanism in which palladium

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alternates between the 0 and +2 oxidation states, a good yield of **2** (75 %) is also obtained if the reaction is initiated with [Pd<sub>2</sub>(dba)<sub>3</sub>] (2.5 mol %),<sup>[18]</sup> a palladium(0) catalyst source.

The qualitative observation of higher activities at lower catalyst loading, together with eventual catalyst inactivation, implicates a competition between catalytic turnover (e.g., step III) and irreversible inactivation of the catalyst (step V).<sup>[19]</sup> Pyridine may promote catalytic turnover by enhancing this branching in favor of step III. The pyridine/[Pd(OAc)<sub>2</sub>] stoichiometry of 2:1 in Scheme 2 reflects the optimal ratio determined experimentally; however, up to six equivalents could be added with only a small decrease in yield (≤5 %).<sup>[20]</sup>

This catalyst system proved to be effective for a series of related substrates (Table 1). Although most of the examples utilize *p*-toluenesulfonamide-substituted starting materials, the reactions of synthetically more attractive *o*-nitrobenzenesulfonamide (Ns) and benzyl carbamate (Cbz) derivatives of 1-amino-4-hexene also proceed in good yield, albeit with longer reaction times (Table 1, entry 1).

Table 1. Intramolecular Oxidative Amination of Olefinic Substrates.<sup>[a]</sup>

| Entry | Substrate | $t$ [h]                                     | Product <sup>[b]</sup> | Yield <sup>[c]</sup> |
|-------|-----------|---------------------------------------------|------------------------|----------------------|
| 1     |           | 2<br>R = Ts<br>8<br>R = Ns<br>48<br>R = Cbz |                        | 87<br>87<br>76       |
| 2     |           | 1.5                                         |                        | 81 (7:3)             |
| 3     |           | 2                                           |                        | 94 (1:1)             |
| 4     |           | 2                                           |                        | 91                   |
| 5     |           | 16                                          |                        | 60                   |
| 6     |           | 1.5                                         |                        | 91                   |

[a] Reaction Conditions: substrate (0.1 mmol), [Pd(OAc)<sub>2</sub>] (5 μmol), pyridine (10 μmol), O<sub>2</sub> (1 atm), xylenes (1 mL), 80 °C. [b] All products were isolated and identified by comparison with published <sup>1</sup>H NMR spectral data.<sup>[4d, 9c]</sup> [c] GC yields (internal standard: anthracene). Entries 1 (R = Ts), 4, and 6 were scaled up (0.8–3 mmol) and the isolated products were obtained in somewhat lower yields: 81, 84, and 87%, respectively.

The products of these reactions diverge between tosyl enamides and allylic tosylamides, although both arise from initial 5-exo cyclization (step I, Scheme 2). Whenever possible, β-hydride elimination (step II) occurs remotely from the tosylamide group to yield an allylic amide product (Table 1, entries 1, 4, and 6). If this path is not available (Table 1, entries 2, 3, and 5), the enamide is formed. In the latter cases, kinetically formed exo methylene products slowly isomerize under the reaction conditions to the more stable internal olefin products.

The present studies demonstrate the versatility and remarkable activity of the [Pd(OAc)<sub>2</sub>]/pyridine catalyst system

in aerobic oxidation catalysis, specifically for the intramolecular oxidative amination of olefins. The selective formation of allylic amides by means of oxidative cyclization provides an attractive, atom-economical alternative to allylic substitution reactions.<sup>[21]</sup> Furthermore, the intermediacy of alkyl palladium(II) species in these reactions raises the possibility of tandem reactions to create more complex heterocyclic structures.<sup>[22]</sup> The distinct simplicity of this catalyst system renders it amenable to high-throughput screening studies to evaluate alternative ligands and other reaction parameters. Specifically, the use of chiral ligands might permit asymmetric C–N bond formation.<sup>[13]</sup>

## Experimental Section

General procedure (cyclization of **1**): (*E*)-4-hexenyltosylamide (25.3 mg, 0.1 mmol), pyridine (0.8 μL, 0.01 mmol; 16.7 mM stock solution in xylene), anthracene (1.78 mg, 0.01 mmol; 16.7 mM stock solution in xylene), xylene (150 μL, Aldrich), and a teflon coated stirrer bar were added to a 13 × 100-mm disposable culture tube. The tube was placed in one of the ports of a Radleys 12-place carousel reaction station with reflux head. After purging the headspace with molecular oxygen, [Pd(OAc)<sub>2</sub>] (1.1 mg, 0.005 mmol; 2.08 mM stock solution in xylene) was added just prior to heating to 80 °C. The total reaction volume was 1 mL. Reaction progress was monitored by gas chromatography (Shimadzu GC-17A gas chromatograph).

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- [19] Step III should exhibit a first-order dependence on [Pd], whereas catalyst inactivation should exhibit a bimolecular or higher order dependence on [Pd]. Consequently, enhanced turnover numbers and frequencies are expected at lower catalyst concentrations. For recent mechanistic characterization of the beneficial effect of reduced catalyst loading in aerobic oxidation reactions, see ref. [9]. See also, T. Rosner, J. Le Bars, A. Pfaltz, D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, 123, 1848–1855.
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## ZEKE Photoelectron Spectroscopy of the *cis* and *trans* Isomers of Formanilide\*\*

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Cationic states are involved in long-range charge transfer in polypeptides,<sup>[1]</sup> an area of intense chemical interest.<sup>[2]</sup> While a number of theoretical and time-resolved studies have contributed to our mechanistic understanding of this problem,<sup>[1]</sup> there is currently little spectroscopic information available for cationic amides.<sup>[3, 4]</sup> Basic questions regard the preference for *cis* or *trans* conformations and barrier heights for interconversion. Here we present initial results that indicate that zero electron kinetic energy (ZEKE) spectroscopy,<sup>[5, 6]</sup> a high-resolution variant of photoelectron spectroscopy, may represent a powerful technique for obtaining vibrationally resolved spectra of cationic amides and model peptides. Spectra are presented for both the *cis* and *trans* isomers of formanilide, an aromatic molecule with an amide side chain. The aromatic group provides a convenient chromophore, while significant charge delocalization occurs from the aromatic ring to the functional group in the cation, so that formanilide is a useful model system for studying the properties of cationic amides.

Local-minimum geometric structures of the neutral ( $S_0$ ) and cationic ( $D_0$ ) isomers of formanilide obtained from MP2(fc)/6-31G\* ab initio calculations are presented in Figure 1.<sup>[7]</sup> For *trans*-formanilide, the calculations predict that the molecule

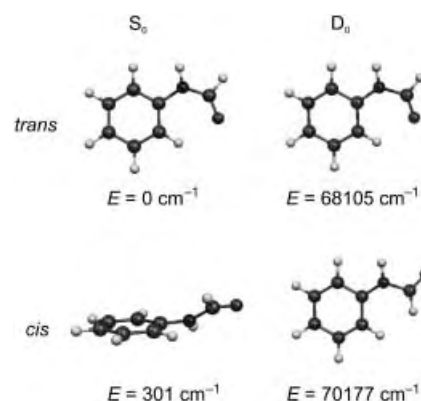


Figure 1. Optimized structures of the neutral ( $S_0$ ) and cationic ( $D_0$ ) isomers of formanilide at the MP2(fc)/6-31G\* level of theory illustrating the ionization-induced geometry changes. Total energies are given relative to the energy of the  $S_0$  state of *trans*-formanilide (–399.693829 Hartree).

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adopts a planar,  $C_s$ -symmetry structure in both the  $S_0$  and  $D_0$  states. The primary ionization-induced structural change for *trans*-formanilide is centered on the N–C<sub>amide</sub> bond, which contracts from 1.4352 to 1.4286 Å. In addition, the amide oxygen atom moves towards the aromatic ring, whereby the C<sub>1</sub>–N–C<sub>amide</sub> bond decreases by 1.5°. *cis*-Formanilide also adopts a planar,  $C_s$ -symmetric structure in the  $D_0$  state, although the neutral molecule corresponds to a nonplanar,  $C_1$  structure in which the amide side chain is twisted relative to the phenyl ring ( $\tau_{C_2-C_1-N-C} = 42^\circ$ ). The conformational preference for planar cationic structures suggests that both isomers are stabilized by resonance structures involving the nitrogen lone pair. A natural population analysis of partial charge distribution revealed that about 20% of the excess positive charge is delocalized to the side chain in the cation.<sup>[8, 9]</sup>

Figure 2 presents the ZEKE spectrum of *trans*-formanilide recorded via the  $S_1 0^0$  origin transition at  $36004.3 \pm 0.1 \text{ cm}^{-1}$ , the dominant peak in the resonance-enhanced multiphoton ionization (REMPI) spectrum of formanilide.<sup>[10–12]</sup> The lowest

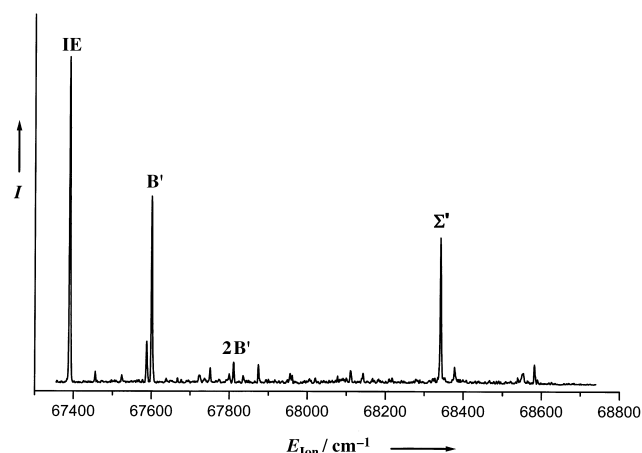


Figure 2. Two-color (1 + 1') ZEKE spectrum of *trans*-formanilide recorded via the  $S_1 0^0$  origin. B' represents the in-plane bend of the side arm, and  $\Sigma'$  a mode containing a high proportion of amide stretch.

energy feature in the ZEKE spectrum occurs at  $67408 \pm 5 \text{ cm}^{-1}$ , and is assigned as the adiabatic ionization energy (IE), since no additional features were evident in scans to lower energy. The IE measured here is consistent with the vertical ionization energy of 8.6 eV ( $69359 \text{ cm}^{-1}$ ) reported for a low-resolution photoelectron spectrum, which contains contributions from both isomers,<sup>[4]</sup> and improves on the value obtained by Mons et al. ( $67430 \pm 20 \text{ cm}^{-1}$ ) using threshold photoionization.<sup>[13]</sup>

Two prominent vibrational features appear in the spectrum of *trans*-formanilide at ion internal energies of 211 and  $952 \text{ cm}^{-1}$ . For  $C_s$ -symmetry molecules, vibrational modes are classified according to whether they transform as  $a'$  or  $a''$  through the plane of symmetry. Since the  $S_0$ ,  $S_1$ ,<sup>[11]</sup> and  $D_0$  states of *trans*-formanilide all have planar geometries, we expect that only  $a'$  modes will appear as strong single-quanta features in the ZEKE spectra. We therefore assign the features at 211 and  $952 \text{ cm}^{-1}$  to an in-plane side-arm bend (B') and a mode involving a significant proportion of amide stretch ( $\Sigma'$ ), by comparison with the ab initio results,<sup>[9]</sup> which

predict harmonic frequencies for these modes at 223 and  $1023 \text{ cm}^{-1}$ , respectively. Excitation of the  $\Sigma'$  mode is particularly notable since it indicates that an ionization-induced geometry change occurs at the amide bond, consistent with significant delocalization of excess charge from the aromatic chromophore to the amide side chain in the cation.

Three small features are evident in the ZEKE spectrum in the region below the B' mode at 65, 135, and  $195 \text{ cm}^{-1}$ . They appear to correspond to double-quantum excitation of the C<sub>1</sub>–N torsion, the out-of-plane side-arm bending modes, and a combination mode thereof.<sup>[9]</sup> A detailed analysis of these lower intensity features is beyond the scope of this communication. Nonetheless, their observation suggests that ZEKE spectra of related molecules such as *N*-benzylformamide may also involve torsional excitation and hence facilitate the characterization of torsional potential energy surfaces of cationic amides and peptides.

Weak excitation of the torsional modes of *trans*-formanilide is unsurprising given that the molecule adopts a planar geometry in the  $S_0$ ,  $S_1$ ,<sup>[11]</sup> and  $D_0$  states. The ZEKE spectra of *cis*-formanilide, however, should include torsional vibrational features since the ground-state neutral molecule corresponds to a nonplanar,  $C_1$ -symmetry structure,<sup>[11]</sup> but the cation is planar (Figure 1). While resonant two-color spectroscopy of *cis*-formanilide is a formidable task due to the low intensity of this isomer in the molecular beam,<sup>[10]</sup> it was possible to obtain two-color ZEKE spectra of *cis*-formanilide, and this indicates that strong FC factors exist for  $D_0 \leftarrow S_1$  excitation.

Figure 3a displays the ZEKE spectrum of *cis*-formanilide obtained via the  $S_1 0^0$  origin at  $34904 \pm 0.1 \text{ cm}^{-1}$ . The single feature at  $67710 \pm 5 \text{ cm}^{-1}$  was assigned as the IE since

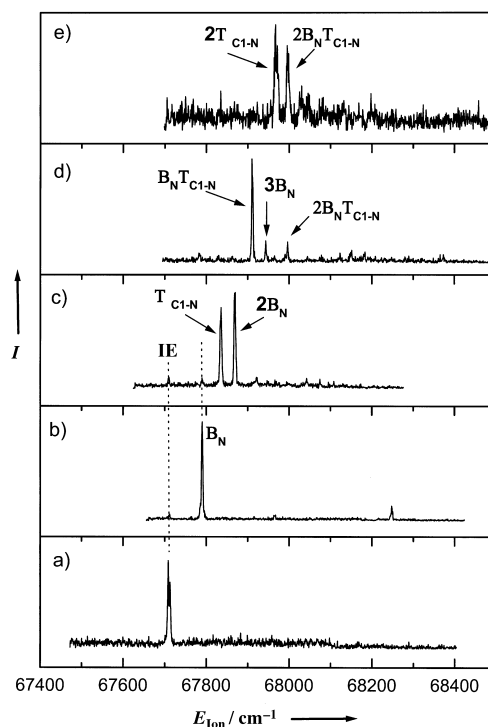


Figure 3. Two-color (1 + 1') ZEKE spectra of *cis*-formanilide recorded via the a)  $S_1 0^0(s)$ , b)  $A_0^1(a)$ , c)  $A_0^2(s) + B_0^1(a)$ , d)  $A_0^3(a) + A_0^1B_0^1(s)$ , and e)  $A_0^4(s) + A_0^2B_0^1(a) + B_0^2(s)$  levels of the  $S_1$  state.<sup>[11]</sup> B<sub>N</sub> represents the out-of-plane side-arm bend, and T<sub>C1-N</sub> the C<sub>1</sub>–N torsional mode.

additional scans to lower energy revealed the presence of no additional features. We note that  $IE_{cis}$  is about  $300\text{ cm}^{-1}$  higher than  $IE_{trans}$ . Since the ab initio results (Figure 1) predict that the *trans* isomer is the lower energy structure in the  $S_0$  state, this indicates that the *cis* conformation is also the higher energy structure in the  $D_0$  state.

Figures 3b–e present ZEKE spectra of *cis*-formanilide recorded via different vibrational levels of the  $S_1$  state. The very limited vibrational structure in all spectra suggests that the FC windows for  $D_0 \leftarrow S_1$  excitation are extremely narrow. However, consideration of the parities of vibrational levels in the  $S_0$ ,  $S_1$ , and  $D_0$  states provides an alternative explanation for the limited vibrational structure evident in these ZEKE spectra. In the nonplanar  $S_0$  state, each torsional level is split into symmetric (s) and antisymmetric (a) components by tunneling through the coplanar potential barrier.<sup>[11]</sup> Both the  $S_1$  and  $D_0$  states have planar equilibrium geometries, and successive torsional levels therefore alternate between s and a parity. Excitation to the  $D_0$  state via an  $S_1$  state with s or a parity should therefore lead to the appearance of s- or a-parity vibrational features, respectively, in the ZEKE spectra.

The  $\Delta\nu = 0$  propensity rule<sup>[5]</sup> and parity considerations were employed to assign each of the strong vibrational features in the ZEKE spectra of *cis*-formanilide (Table 1). Several of the ZEKE spectra display excitation of features with both s and a parity due to the cation being accessed via  $S_1$  bands corresponding to overlapping  $S_1 \leftarrow S_0$  transitions with different parities.<sup>[13]</sup> The ZEKE spectra reveal overtone and combination bands corresponding to excitation of the out-of-plane side-arm bend centered on the N atom ( $B_N$   $80\text{ cm}^{-1}$ ) and the  $C_1$ –N torsion ( $T_{C_1-N}$   $126\text{ cm}^{-1}$ ), consistent with the nonplanar to planar  $D_0 \leftarrow S_0$  geometry change predicted by the calculations. The out-of-plane bend and  $C_1$ –N torsion are predicted to occur at 52 and  $96\text{ cm}^{-1}$  at the MP2/6-31G\* level of theory, in reasonable agreement with the experimental values. Finally, it is of interest to note that unexpected parity transitions are evident as low-intensity features in the spectra (e.g., the IE feature in Figure 3b).

In summary, spectra of *cis*- and *trans*-formanilide demonstrate that the system is amenable to study by ZEKE spectroscopy. The spectrum of *trans*-formanilide is dominated by excitation of the in-plane side-arm bend ( $211\text{ cm}^{-1}$ ) and amide stretch ( $952\text{ cm}^{-1}$ ), while the spectra of the *cis* isomer contain overtones and combinations of the out-of-plane side-

arm bend ( $80\text{ cm}^{-1}$ ) and the  $C_1$ –N torsion ( $126\text{ cm}^{-1}$ ). The observation of these modes is in line with planar geometries for both isomers in the  $D_0$  state. Accurate ionization energies were obtained and allowed us to assign the *trans* isomer as the lower energy conformation of the cation. While some of the results presented above are characteristic of the direct attachment of the amide group to the phenyl ring in formanilide (e.g., excitation of  $B'$  in the *trans*-formanilide cation), they demonstrate that ZEKE spectroscopy can productively be applied to obtain vibrationally resolved, conformationally selective spectra of amides and model peptides, and should be a highly useful tool for future studies of these systems.

## Experimental Section

The experimental apparatus and techniques employed in this work have been described in detail previously.<sup>[5,6,14]</sup> Formanilide (Aldrich, 99% purity) was heated to  $140^\circ\text{C}$  and seeded in Ne carrier gas at 2 bar from a sample holder located immediately behind the valve (0.8-mm nozzle).

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Table 1. Frequencies [ $\text{cm}^{-1}$ ] of vibrational features observed in the ZEKE spectra of *cis*-formanilide via different intermediate  $S_1$  states.<sup>[a]</sup>

| $S_1 0^0(s)$ | $A_0^1(a)$ | $A_0^2(s) + B_0^1(a)$ | $A_0^3(a) + A_0^1B_0^1(s)$ | $A_0^4(s) + A_0^2B_0^1(a) + B_0^2(s)$ | Assignment           |
|--------------|------------|-----------------------|----------------------------|---------------------------------------|----------------------|
| 0            | 0          | 0                     | –                          | –                                     | IE (s)               |
| –            | 80         | 80                    | 80                         | –                                     | $B_N$ (a)            |
| –            | –          | 126                   | –                          | –                                     | $T_{C_1-N}$ (a)      |
| –            | –          | 158                   | –                          | –                                     | $2B_N(s)$            |
| –            | –          | 213                   | 208                        | –                                     | $B_N T_{C_1-N}$ (s)  |
| –            | –          | –                     | 241                        | –                                     | $3B_N$ (a)           |
| –            | –          | –                     | 262                        | 262                                   | $2T_{C_1-N}$ (s)     |
| –            | –          | –                     | 294                        | 294                                   | $2B_N T_{C_1-N}$ (a) |

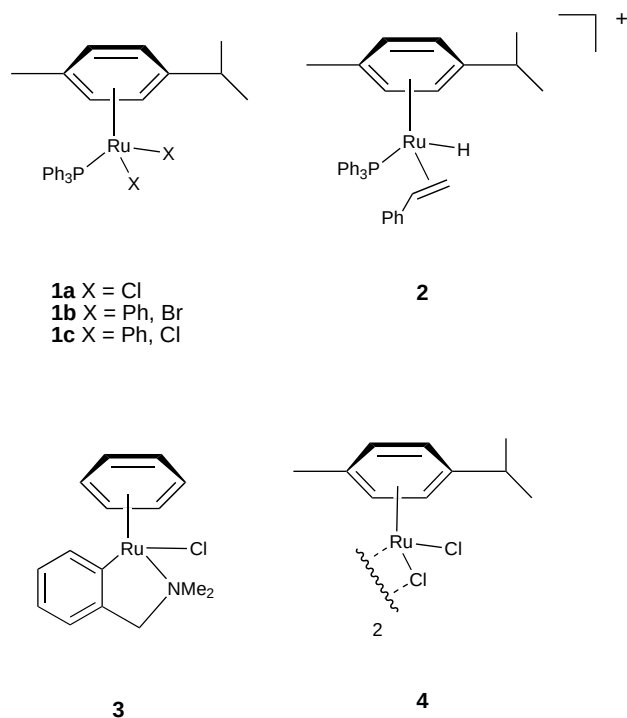
[a] Frequencies are given relative to the IE, and parities are denoted as s (symmetric) and a (antisymmetric).  $S_1$  state assignments and notation follow ref. [11].  $B_N$  represents the out-of-plane side-arm bending mode, and  $T_{C_1-N}$  the  $C_1$ –N torsion.

# Ruthenium-Catalyzed Oxidative Heck Reactions\*\*

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C. F. J. Barnard, and E. Rowsell

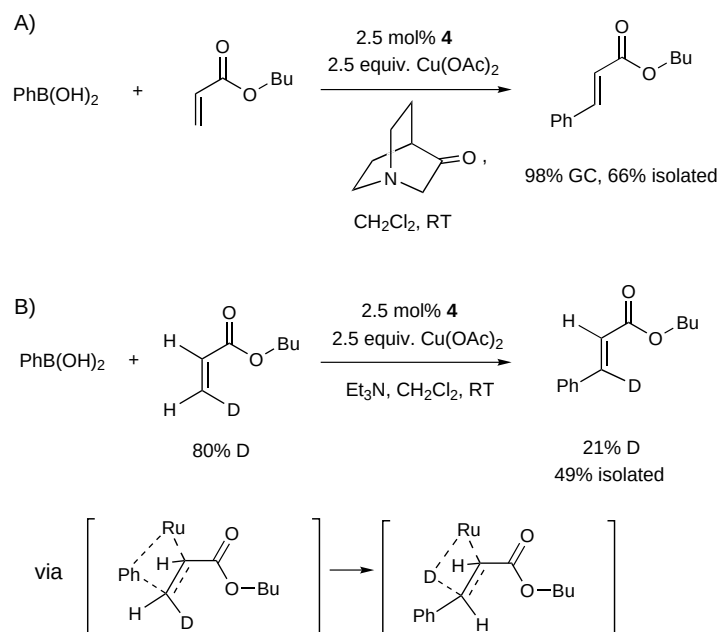
The coupling of organic electrophiles with alkenes is one of the cornerstones of Pd complex catalysis. The basis of the chemistry involved lies in early contributions by Mizoroki<sup>[1]</sup> and Heck.<sup>[2]</sup> Many of Heck's examples involve stoichiometric reactions of organomercurials and other potential organic nucleophiles in addition to Pd salts. Since then, but with a notable recent exception (see below),<sup>[3]</sup> palladium complexes have been used essentially exclusively in Heck catalysis.

Ruthenium complexes are readily accessible, but less widely utilized in the catalysis of C–C coupling reactions.<sup>[4]</sup> Faller and Chase demonstrated that complex **1b**, prepared from the dichloride **1a** and PhMgBr, reacted with ethene and AgSbF<sub>6</sub> to form styrene and the corresponding Ru–H complex **2**.<sup>[5]</sup> An intramolecular variant through insertion of ethene into the Ru–C bond of complex **3** was reported by Pfeffer and co-workers.<sup>[6]</sup> These stoichiometric reactions



provided the key to catalysis, since reversion from a Ru–H complex to the halide together with a compatible method for the formation of a Ru–C bond would, in principle, complete the cycle.

In preliminary experiments it was established that the reaction of **1a** with PhSnBu<sub>3</sub> or PhB(OH)<sub>2</sub> occurred readily to give **1c** as a stable product.<sup>[7]</sup> This observation formed the basis of a successful stoichiometric reaction between PhB(OH)<sub>2</sub> and methyl propenoate, promoted by complex **1a** in the presence of NEt<sub>3</sub> under mild conditions. The use of more than 2 equivalents of Cu(OAc)<sub>2</sub> to reoxidize the expected Ru–H complex led to catalytic turnover; the process was more efficient when PPh<sub>3</sub> was omitted from the initial Ru catalyst (Scheme 1).<sup>[8]</sup> Optimization experiments



Scheme 1. Ruthenium-catalyzed Heck reactions: A) optimum conditions; B) with stereospecifically labeled butyl propenoate.

demonstrated that other oxidizing agents (e.g. Me<sub>3</sub>NO, Fremy's salt) also promoted the reaction, but less effectively than Cu<sup>II</sup>. Significant improvements in the base component were achieved by this approach: 3-quinuclidone gave the highest turnover (Scheme 1 A). The conditions were successfully applied with *n*-butyl propenoate and other ArB(OH)<sub>2</sub> species (Ar = *p*-CHO, OMe, OCF<sub>3</sub>).

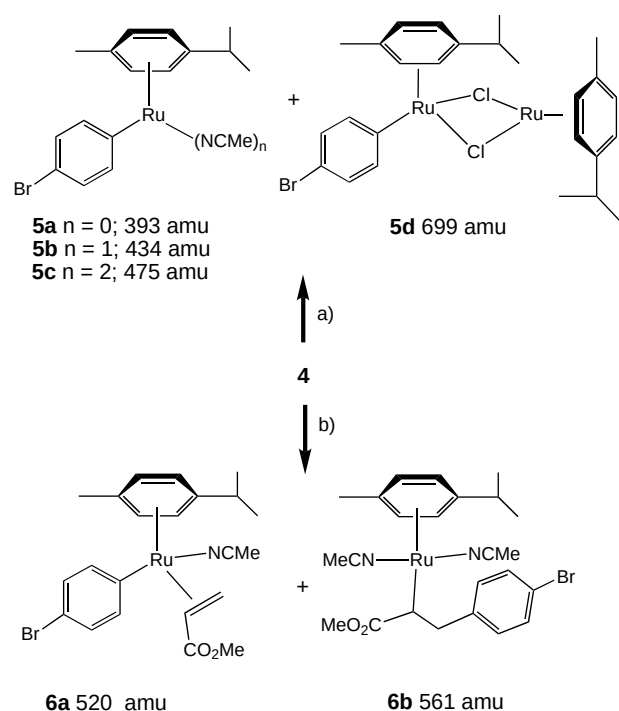
To compare the pathway with the more familiar Pd case, the addition of PhB(OH)<sub>2</sub> to butyl (*Z*)-3-D-propenoate<sup>[9]</sup> was effected (Scheme 1 B). The label was largely, but not completely, absent in the product. This is in accord with partial stereoselectivity in the catalytic process, most probably through stereospecific *cis* addition of Ru–Ph<sup>[10]</sup> to the alkene followed by some randomization (Ru keto-enol equilibria?)<sup>[11]</sup> prior to stereospecific Ru–H/D *cis* elimination. Electrospray mass spectrometry revealed intermediates in the catalytic cycle, best observed with 4-BrC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> in a CH<sub>3</sub>CN matrix (Scheme 2). Before the addition of the alkene, three monomeric complexes **5a–c** and one dimeric cationic complex **5d** can be characterized on the basis of the typical

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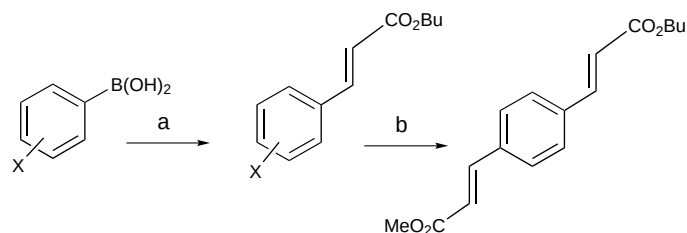
[\*\*] We thank the EPSRC for CASE support (to E.J.F.) with Johnson Matthey, who also provided the Ru salts. Dr. R. T. Aplin was very helpful in acquiring electrospray mass spectra.

Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 2. Cationic species observed by electrospray mass spectrometry recorded on a Micromass BioQ II-ZS at a cone voltage of +20 V, Ru-102, Br-81, Cl-35 ion specified. Reagents and conditions: a)  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  ( $3.26 \times 10^{-5}$  mol), *p*-bromobenzenboronic acid ( $3.26 \times 10^{-5}$  mol),  $\text{NEt}_3$  ( $3.26 \times 10^{-5}$  mol), MeCN (20 mL), 30 min, room temperature; b) same conditions as (a), but allowed to stand with a tenfold excess of methyl propenoate for 15 h at  $-20^\circ\text{C}$  before assay.

isotope distributions in the parent molecular ion. In the presence of methyl propenoate, the same set of monomeric ions are observed together with two distinct new halide-free species, corresponding to monoalkene complexes with one or two coordinated acetonitrile ligands. The simplest representation in which these preserve an 18e configuration at the ruthenium center is as the aryl and alkyl complexes **6a** before, and **6b** after the expected migration step; ring slippage is an alternative possibility.<sup>[12]</sup> The nature of propenoate binding



Scheme 3. Ru-catalyzed reactions of haloaryl boronic acids. Reagents and conditions: a) boronic acid (0.4 mmol),  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  (6.2 mg, 0.02 mmol),  $\text{Cu}(\text{OAc})_2$  (201 mg, 1 mmol), quinuclidin-3-one (126 mg, 1 mmol), and butyl propenoate (155 mg, 1.2 mmol), toluene, 24 h, room temperature,  $\text{X} = m\text{-Cl}$  (77 %),  $\text{X} = p\text{-Cl}$  (93 %),  $\text{X} = p\text{-Br}$  (63 %),<sup>[13]</sup>  $\text{X} = m\text{-Br}$  (96 %),  $\text{X} = m\text{-I}$  (76 %),  $\text{X} = p\text{-I}$  (77 %); b) butyl *p*-iodocinnamate (50 mg, 0.15 mmol), tris(*o*-tolyl)phosphane (4.56 mg, 0.015 mmol),  $\text{Pd}_2(\text{dba})_3$  (7.8 mg, 0.0076 mmol), methyl propenoate (65 mg, 0.76 mmol), triethylamine (76 mg, 0.76 mmol), DMF, 24 h, room temperature, **10** (90 %); dba = *trans*,*trans*-dibenzylideneacetone, DMF = *N,N*-dimethylformamide. For product characterization, see Supporting Information.

demonstrate the generality of the selective C–B activation and transfer. Good yields are maintained over a range of boronic acids substituted with Cl, Br, or I. In one case, a tandem Pd- and Ru-catalyzed coupling reaction in which C–B is activated first, followed by C–X, gave the unsymmetrical phenylene-bis-propenoate **10**.<sup>[14]</sup>

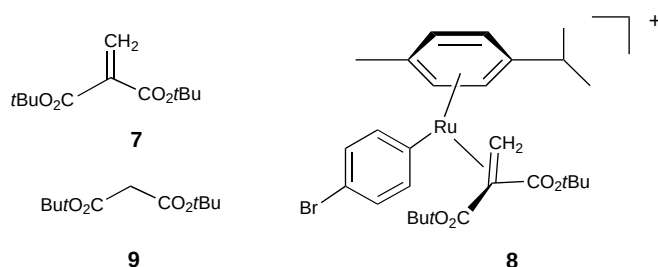
In related work, it was demonstrated that aryl stannanes,<sup>[15]</sup> aryl silanols,<sup>[16]</sup> and aryl boronic acids<sup>[17]</sup> can be coupled with electrophilic alkenes under  $\text{Pd}(\text{OAc})_2$  catalysis (5–10 mol %). In the first two cases  $\text{Cu}^{\text{II}}$  is present as a reoxidant. In the last case, the authors favor, but do not prove, an oxidative addition of  $\text{ArB}(\text{OH})_2$  as the initial step; the reaction works only in AcOH. Very recently, Lautens and co-workers observed the coupling of styrenes with an excess of functionally diverse boronic acids in aqueous solution, to form *E* stilbenes in the absence of a formal oxidant.<sup>[3]</sup> The relationship of these procedures to ours is intriguing, but as yet unclear.

The synthetic potential of the ruthenium Heck reaction is being actively investigated further.<sup>[18]</sup>

## Experimental Section

**Butyl (*E*)-3-bromocinnamate:** 3-bromobenzenboronic acid (81 mg, 0.4 mmol),  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  (6.2 mg, 0.02 mmol),  $\text{Cu}(\text{OAc})_2$  (201 mg, 1 mmol), and 3-quinuclidinone (126 mg, 1 mmol) were combined in a dry Schlenk tube, which was sealed and placed under vacuum for 30 min. The Schlenk tube was flushed with argon, and butyl propenoate (155 mg, 1.2 mmol) and freshly distilled toluene (10 mL) were added through a syringe. The reaction mixture was stirred for 24 h at ambient temperature. The volatile components were removed in vacuo, and the product was purified by flash column chromatography on silica gel (diethyl ether) to give butyl (*E*)-3-bromocinnamate (112 mg, 96 %). M.p.  $36^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.96$  (3H, t,  $J = 7.3$  Hz;  $\text{CH}_3$ ), 1.44 (2H, m;  $\text{CH}_2$ ), 1.70 (2H, m;  $\text{CH}_2$ ), 4.22 (2H, t,  $J = 6.7$  Hz;  $\text{OCH}_2$ ), 6.46 (1H, d,  $J = 16$  Hz; H1), 7.26 (1H, dd,  $J = 8$  Hz and 7.95 Hz; H5'), 7.46 (1H, d,  $J = 8$  Hz; H4'), 7.52 (1H, d,  $J = 7.95$  Hz; H6'), 7.61 (1H, d,  $J = 16$  Hz; H3), 7.68 (1H, s; H2');  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta = 13.6$  ( $\text{CH}_3$ ), 19.1 ( $\text{CH}_2$ ), 30.6 ( $\text{CH}_2$ ), 64.5 ( $\text{OCH}_2$ ), 119.7 (C2), 122.9, 126.5, 130.3, 130.6, 132.9, 136.4, (C1', C2', C3', C4', C5', C6'), 142.7 (C3) 166.5 (C1); IR (Nujol):  $\tilde{\nu}_{\text{max}} = 2920.9$ , 1727.3 (C=O), 1641.7  $\text{cm}^{-1}$  (C=C); HR-MS: calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Br}$ : 283.0335, found: 283.0335; MS (atmospheric pressure chemical ionisation; APCI +):  $m/z$  (%): 284 [ $\text{MH}^+$ ], 226 [ $\text{M} - \text{Bu}$ ].

**Coupling of butyl (*Z*)-3-D-propenoate:** Benzenboronic acid (10 mg,  $8.2 \times 10^{-5}$  mol),  $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$  (1.25 mg,  $4.1 \times 10^{-7}$  mol), and  $\text{Cu}(\text{OAc})_2$  (40.9 mg, 0.21 mmol) were combined in a vial, and THF (0.9 mL) and



was explored through the use of methylene malonate **7**, which gave rise to a strong acetonitrile-free molecular ion **8** for the coordinated alkene complex, under conditions in which the parent malonate **9** remains passive.

The inertness of the aryl bromide residue towards ruthenium (i.e. dominance of nucleophilic attack by the boronic acid) indicated valuable synthetic potential. Several haloaryl boronic acids were subjected to our best conditions of catalytic turnover, with *n*-butyl propenoate as the alkene component. The results are recorded in Scheme 3, and

triethylamine (0.1 mL) were added. Butyl (*Z*)-3-D-propenoate was added through a syringe. The vial was sealed, and the reaction mixture was stirred at ambient temperature for 17 h. The solvent was removed in vacuo, and the product was purified by filtration through a short plug of silica gel (diethyl ether) to afford butyl (*E*)-cinnamate (8.2 mg, 49%). B.p. 280–284 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 0.99 (3 H, t, *J* = 7.3 Hz; CH<sub>3</sub>), 1.43 (2 H, m; CH<sub>2</sub>), 1.72 (2 H, m; CH<sub>2</sub>), 4.23 (2 H, t, *J* = 6.7 Hz; OCH<sub>2</sub>), 6.48 (1 H, d, *J* = 16 Hz; H<sub>2</sub>), 7.40 (3 H, m; ArH), 7.53 (2 H, m; ArH), 7.77 (1 H, d, *J* = 16 Hz; H<sub>3</sub>); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>): δ = 13.6 (CH<sub>3</sub>), 19.1 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 64.3 (OCH<sub>2</sub>), 118.2 (C2), 127.9, 128.7, 130.1, 134.3, (Ar-C), 144.4 (C3), 167.0 (C1); UV/Vis:  $\tilde{\nu}_{\text{max}}$  (MeOH) = 276 nm ( $\epsilon$  = 22 000); MS (CI<sup>+</sup>): *m/z* (%): 205 [MH<sup>+</sup>].

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## Enantiopure Double-Helical Alkynyl Cyclophanes

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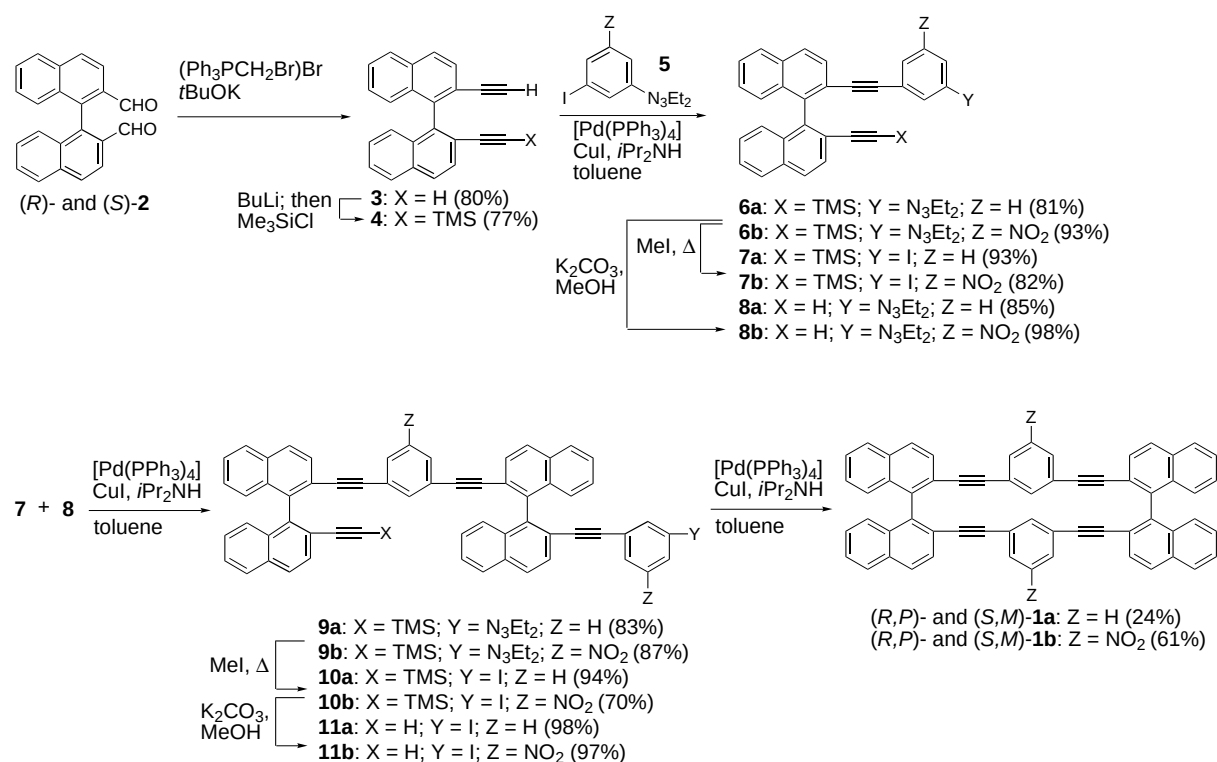
Chiral  $\pi$ -conjugated molecules have been the subject of extensive investigation from the standpoints of structural chemistry and material science.<sup>[1]</sup> Double-helical molecules, in particular, are of great interest on account of their unique structural features as well as potential applications in optics and electronics. Several twisted alkynyl cyclophanes have been reported, but, unfortunately, they were obtained as racemates.<sup>[2,3]</sup> To the best of our knowledge, only one nonracemic double-helical molecule has been prepared. Namely, a cyclophane was synthesized by connecting a (+)-2,15-diethynyl[6]helicene auxiliary with *ortho*-phenylene bridges.<sup>[4]</sup> However, this synthesis was rather lengthy, and only one enantiomer was obtained. Moreover, in the key coupling of the helicene with an *o*-diiodobenzene unit, the target molecule was obtained in less than 3 % yield. We report here on a rational synthesis and full characterization of double-helical alkynyl cyclophanes **1** of both enantiopure forms.<sup>[5]</sup>

The synthetic route is shown in Scheme 1. Separately (*R*)- and (*S*)-2,2'-diformyl-1,1'-binaphthyl (**2**)<sup>[6]</sup> underwent carbon–carbon coupling, and the resulting diethynyl compound **3** was converted to the monosilyl ethynyl derivative **4**. Exposure of this compound to an aryl iodide with the diethyltriazene function **5** afforded **6**. The triazene derivatives **6** were transformed into iodides **7** or desilylated to give **8**.<sup>[7]</sup> Sonogashira coupling<sup>[8]</sup> of **7** with **8** furnished **9**. After conversion of **9** to **11** via **10** through successive functional group transformations, intramolecular Sonogashira coupling provided the desired cyclophanes **1** in enantiopure form (Table 1). These compounds formed white needlelike crystals upon recrystallization, but none of them were suitable for X-ray analyses. Then, we prepared racemic **1b** by mixing equimolar amounts of (*R,P*)- and (*S,M*)-**1b**. Recrystallization of this mixture from CH<sub>2</sub>Cl<sub>2</sub>/hexane furnished crystals conducive to X-ray crystallographic analysis.<sup>[9]</sup>

As is evident from the ORTEP view depicted in Figure 1, the cyclophane skeleton is twisted, resulting in the double-helical motif. The C≡C bonds are slightly deformed from linearity. Notably, the two binaphthyl groups differ significantly in the dihedral angle defined by the naphthalene planes (68° and 78°, respectively). The space-filling model (Figure 2) indicates that the symmetrical structure places the inside hydrogen atoms of the phenylene rings very close to each other. The resulting ring strain is passed on unsymmetrically into the binaphthyl termini in the crystal.

In contrast to the solid-state molecular structure, <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1** (Table 1) are compatible with a single

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Scheme 1. Synthesis of **1**. TMS = trimethylsilyl.

Table 1. Selected physical data of compounds **1**.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| <p><b>1a</b>: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 6.89–6.94 (m, 6H), 7.05 (d, <i>J</i> = 8.6 Hz, 4H), 7.21 (t, <i>J</i> = 7.0 Hz, 4H), 7.42 (t, <i>J</i> = 7.0 Hz, 4H), 7.76 (d, <i>J</i> = 8.6 Hz, 4H), 7.86 (d, <i>J</i> = 8.6 Hz, 4H), 7.87 (d, <i>J</i> = 8.6 Hz, 4H), 7.92 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 90.4, 92.1, 121.7, 123.6, 126.4, 126.7, 126.8, 128.1 (2C), 128.2, 129.2, 129.6, 132.7, 133.0, 136.9, 138.6; MS (positive-ion matrix-assisted laser desorption/ionization (MALDI)): [<i>M</i><sup>+</sup>] calcd 752.25, found 752.3. (<i>R</i>) isomer: [<i>α</i>]<sub>D</sub><sup>20</sup> = +690.4 (<i>c</i> = 1.0 in CHCl<sub>3</sub>); [<i>M</i>]<sub>D</sub> = +5198.2; UV/Vis (CHCl<sub>3</sub>, 2.7 × 10<sup>−6</sup> M): λ<sub>max</sub> (ε<sub>max</sub>) = 240 (1.0 × 10<sup>5</sup>), 255 (9.2 × 10<sup>4</sup>), 278 (9.4 × 10<sup>4</sup>), 302 nm (6.4 × 10<sup>4</sup>); CD (CHCl<sub>3</sub>, <i>c</i> = 2.4 × 10<sup>−6</sup> M, 1.0-cm cell): 275 (θ = −13.5, Δε = −171.4), 301 nm (θ = 12.4, Δε = 157.5); solid-state CD (Nujol mull): 272 (θ = −13.9), 301 nm (θ = 11.3). (<i>S</i>) isomer: [<i>α</i>]<sub>D</sub><sup>20</sup> = −713.2 (<i>c</i> = 0.89 in CHCl<sub>3</sub>); [<i>M</i>]<sub>D</sub> = −5369.3; UV/Vis (CHCl<sub>3</sub>, <i>c</i> = 2.7 × 10<sup>−6</sup> M): λ<sub>max</sub> (ε<sub>max</sub>) = 240 (1.3 × 10<sup>5</sup>), 254 (1.1 × 10<sup>5</sup>), 278 (1.1 × 10<sup>5</sup>), 303 nm (7.2 × 10<sup>4</sup>); CD (CHCl<sub>3</sub>, <i>c</i> = 2.7 × 10<sup>−6</sup> M, 1.0-cm cell): 273 (θ = 19.3, Δε = 220.1), 300 nm (θ = −16.6, Δε = −189.0); solid-state CD (Nujol mull): 272 (θ = 13.4), 301 nm (θ = −13.0)</p> <p><b>1b</b>: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.07 (d, <i>J</i> = 8.6 Hz, 4H), 7.30 (t, <i>J</i> = 7.5 Hz, 4H), 7.52 (t, <i>J</i> = 7.5 Hz, 4H), 7.79 (d, <i>J</i> = 8.6 Hz, 4H), 7.83 (s, 4H), 7.96 (d, <i>J</i> = 8.6 Hz, 4H), 8.00 (d, <i>J</i> = 8.6 Hz, 4H), 8.04 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 89.5, 93.0, 120.3, 124.1, 125.2, 126.8, 127.0, 127.1, 128.2, 128.6, 128.7, 132.5, 133.2, 138.9, 141.7, 148.0; MS (electrospray ionization (ESI)): [<i>M</i><sup>+</sup>] calcd 842.2, found 842.2. (<i>R</i>) isomer: [<i>α</i>]<sub>D</sub><sup>20</sup> = +436.6 (<i>c</i> = 0.98 in CHCl<sub>3</sub>); [<i>M</i>]<sub>D</sub> = +3680.0; UV/Vis (CHCl<sub>3</sub>, <i>c</i> = 2.4 × 10<sup>−6</sup> M): λ<sub>max</sub> (ε<sub>max</sub>) = 239 (1.3 × 10<sup>5</sup>), 264 (1.1 × 10<sup>5</sup>), 301 nm (6.4 × 10<sup>5</sup>); CD (CHCl<sub>3</sub>, <i>c</i> = 2.7 × 10<sup>−6</sup> M, 1.0-cm cell): 254 (θ = −8.7, Δε = −98.9), 297 nm (θ = 6.7, Δε = 76.7); solid-state CD (Nujol mull): 242 (θ = −9.7), 307 nm (θ = 3.2). (<i>S</i>) isomer: [<i>α</i>]<sub>D</sub><sup>20</sup> = −461.4 (<i>c</i> = 0.99 in CHCl<sub>3</sub>); [<i>M</i>]<sub>D</sub> = −3888.8; UV/Vis (CHCl<sub>3</sub>, 2.3 × 10<sup>−6</sup> M): λ<sub>max</sub> (ε<sub>max</sub>) = 238 (1.2 × 10<sup>5</sup>), 263 (1.1 × 10<sup>5</sup>), 306 nm (6.7 × 10<sup>4</sup>); CD (CHCl<sub>3</sub>, <i>c</i> = 1.2 × 10<sup>−4</sup> M, 0.2 mm cell): 255 (θ = 10.7, Δε = 139.0), 296 nm (θ = −7.6, Δε = −98.6)</p> |
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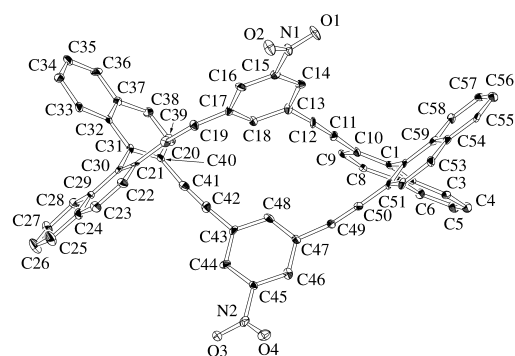


Figure 1. Structure of **1b** in crystals of **1b** · 2CH<sub>2</sub>Cl<sub>2</sub>; ellipsoids drawn at the 50% probability level. Hydrogen atoms and CH<sub>2</sub>Cl<sub>2</sub> were omitted for clarity. Selected interatomic distances [Å] and angles [°]: C10–C11 1.446(8), C11–C12 1.229(8), C12–C13 1.427(8), C17–C19 1.423(8), C19–C20 1.239(9), C20–C21 1.423(8), C40–C41 1.441(9), C41–C42 1.199(9), C42–C43 1.427(9), C47–C49 1.431(8), C49–C50 1.220(8), C50–C51 1.430(8); C9–C10–C11 117.2(5), C10–C11–C12 176.2(6), C11–C12–C13 177.2(7), C12–C13–C14 120.6(5), C16–C17–C19 121.5(5), C17–C19–C20 170.4(6), C19–C20–C21 173.6(6), C20–C21–C22 118.0(6), C39–C40–C41 117.4(5), C40–C41–C42 174.5(6), C41–C42–C43 175.2(6), C42–C43–C44 120.7(5), C46–C47–C49 122.6(6), C47–C49–C50 170.5(6), C49–C50–C51 174.1(6), C50–C51–C52 116.3(5).

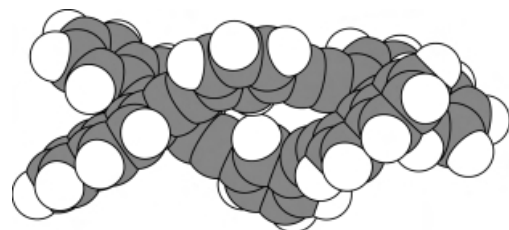


Figure 2. Space-filling model of double-helical cyclophane **1a**.

symmetrical species. With decreasing temperature, the  $^1\text{H}$  NMR signals shift to lower field and broaden to some extent. No unsymmetrical patterns corresponding to the strained structure were observed, which is indicative of rapid fluctuation of the cyclophane frameworks in solution.

The chirality of **1** is reflected unambiguously by its optical properties. The  $[\alpha]_{\text{D}}$  values of these compounds are totally different from that of the simple binaphthyldiyne **12** (Table 2). Upon formation of cyclic arylene–ethynylene skeletons, the sign of the optical rotation

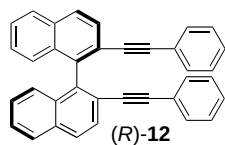


Table 2. Optical properties of **1** and a model compound.

| Compound                  | $[\alpha]_{\text{D}}$ | $c$ [g per 100 mL]        | $T$ [°C] |
|---------------------------|-----------------------|---------------------------|----------|
| ( <i>R</i> )- <b>12</b>   | − 6.91                | 1.01 ( $\text{CHCl}_3$ )  | 30.5     |
| ( <i>R,P</i> )- <b>1a</b> | + 690.42              | 0.995 ( $\text{CHCl}_3$ ) | 29.7     |
| ( <i>S,M</i> )- <b>1a</b> | − 713.15              | 0.89 ( $\text{CHCl}_3$ )  | 29.2     |
| ( <i>R,P</i> )- <b>1b</b> | + 436.59              | 0.98 ( $\text{CHCl}_3$ )  | 29.2     |
| ( <i>S,M</i> )- <b>1b</b> | − 461.36              | 0.99 ( $\text{CHCl}_3$ )  | 30.4     |

reverses and the absolute magnitude increases significantly. As expected, the circular dichroism (CD) spectra of the enantiomers of **1** are opposite in sign but equal in magnitude, and their profiles differ significantly from that of **12** (Figure 3a). The strong Cotton effect in **12** with a zero-point at 320 nm is not observed for **1**, rather a new Cotton effect with a zero-point at 283 nm is observed. The Cotton effect induced in **12** by the ethynylated binaphthyl chromophore is apparently

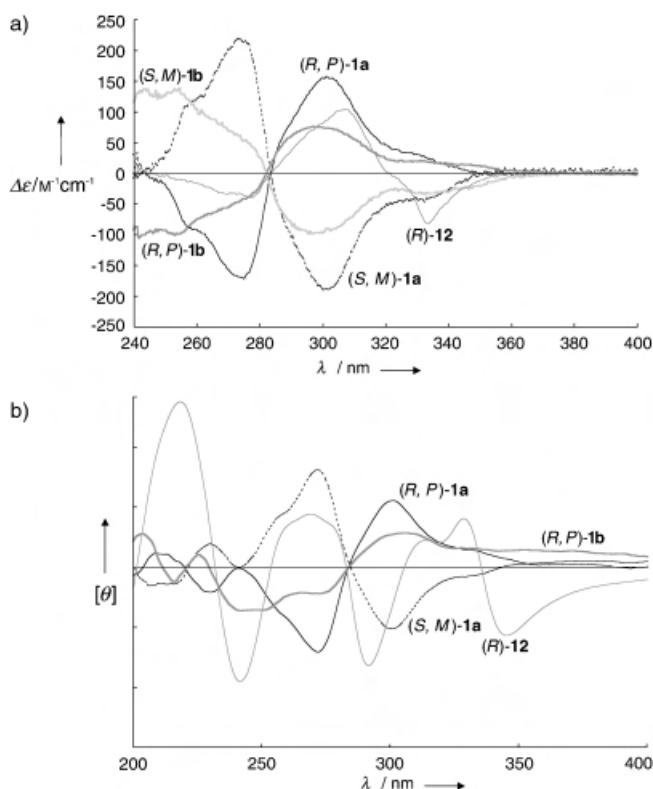


Figure 3. CD spectra of **1a**, **1b**, and **12** a) in  $\text{CHCl}_3$ , b) in Nujol mull.

overcompensated in **1** by the double-helix formation. This finds strong support from CD spectra in the solid state (Figure 3b).<sup>[10]</sup> The analogous profiles observed in the spectra given in Figure 3 imply no essential structural alteration in solution.

We have synthesized unique double-helical alkynyl cyclophanes in enantiopure form and have performed the first successful X-ray crystallographic analysis of this type of compound. Access to both enantiomers allowed full characterization of the chiral double-helical arylene–ethynylene moiety by CD spectra. The utility of solid-state CD spectroscopy is particularly noteworthy. The agreement between solution and solid-state spectra indicates that virtually the same structure occurs both in solution and in the solid state. Thus, once the crystal structure is available, the structure of the nonracemic molecule in solution can be unambiguously elucidated by comparison of CD spectra in both states.

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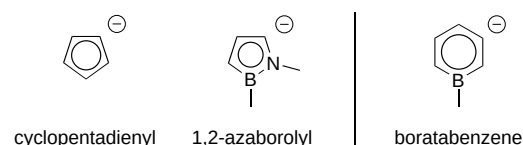
# 1,2-Azaborolyls, Isoelectronic Analogues of the Ubiquitous Cyclopentadienyl Ligand: Synthesis of *B*-Heteroatom-Substituted 1,2-Azaborolyl Complexes and an Assessment of Their Electronic Features\*\*

Shih-Yuan Liu, Michael M.-C. Lo,\* and Gregory C. Fu\*

The cyclopentadienyl group is one of the most widely used ligands in organometallic chemistry, and metal complexes that bear cyclopentadienyl (Cp) ligands have been applied across a broad spectrum of fields.<sup>[1]</sup> One particularly noteworthy use of cyclopentadienyl complexes (e.g., zirconocene- and titanocene-based systems) is as catalysts for Ziegler–Natta polymerizations of olefins.<sup>[2]</sup>

The desire to modulate the reactivity of Ziegler–Natta catalysts has led to growing interest in the development of variations of Cp-based Group 4 metallocenes.<sup>[2, 3]</sup> For example, a number of recent studies have pursued the use of boron-based heterocycles as alternatives to cyclopentadienyl.<sup>[4]</sup> Particularly noteworthy are the investigations of Bazan and Ashe, who have shown that boratabenzene–zirconium complexes can furnish reactivity distinct from cyclopentadienyl–zirconium complexes and that the electronic nature of the boron substituent dictates the catalyst's course of action.<sup>[5–8]</sup>

1,2-Azaborolyls are isoelectronic with cyclopentadienyls (Scheme 1). As with boratabenzenes,<sup>[9]</sup> the boron of azaborolyls provides a potentially straightforward point of attachment for substituents that can modulate the electronic nature of the boron heterocycle.<sup>[10]</sup>



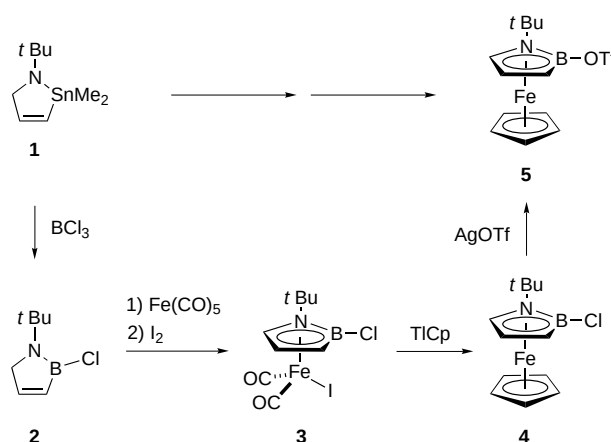
Scheme 1. Cyclopentadienyl and related ligands.

Surprisingly, 1,2-azaborolyls have not been widely investigated. Nearly all of the work to date is due to Schmid, whose pioneering studies of azaborolyls were initiated two decades ago.<sup>[11, 12]</sup> Only two substituents on boron, both of which are carbon-based (methyl and phenyl), have been described.

In 1998, we initiated a program directed at expanding the diversity of accessible 1,2-azaborolyls, with a particular focus on the boron substituent. Herein, we demonstrate that, from a

single precursor, we can synthesize azaborolyl complexes that bear a wide array of substituents (hydrogen, carbon, nitrogen, oxygen, fluorine, phosphorus, and sulfur). We have structurally characterized a B–OR adduct, and through electrochemical studies we have established that the group on boron exerts a significant impact on the electronic nature of the metal complex.

In our initial investigation, we chose to focus on the synthesis of azaborolyl–iron complexes, thereby allowing direct comparison with much-studied, isoelectronic ferrocenes.<sup>[1b]</sup> Transmetalation of the previously reported stannacycle **1**<sup>[13]</sup> with BCl<sub>3</sub> affords the *B*-chloroboracycle **2**, which is then complexed to iron (Scheme 2).<sup>[14]</sup> Treatment of this  $\eta^5$ -(1,2-azaborolyl) adduct **3** with TiCp<sup>[15]</sup> furnishes ferrocene analogue **4**, the chloride of which is then abstracted by AgOTf (OTf = OSO<sub>2</sub>CF<sub>3</sub>) to provide the more reactive triflate complex **5**.<sup>[16]</sup>



Scheme 2. Synthesis of *B*-heteroatom-substituted  $\eta^5$ -(1,2-azaborolyl) complexes.

Complex **5** reacts with anionic nucleophiles to produce a wide array of *B*-substituted adducts **6** in good to excellent yields (Table 1). Organometallic reagents (Table 1, entries 1 and 2), hydride (Table 1, entry 3),<sup>[17]</sup> alkoxides and thiolates

Table 1. Synthesis of a diverse array of *B*-substituted 1,2-azaborolyl complexes by nucleophilic substitution.

| Entry | M–Nu                                     | Yield [%] <sup>[a]</sup> |
|-------|------------------------------------------|--------------------------|
| 1     | Li- <i>n</i> Bu                          | 84                       |
| 2     | MgBr-CH <sub>2</sub> =CH-CH <sub>3</sub> | 88                       |
| 3     | LiAlH <sub>4</sub>                       | 91                       |
| 4     | Na-OMe                                   | 83 <sup>[b]</sup>        |
| 5     | Na-SBn                                   | 89                       |
| 6     | Li-NMe <sub>2</sub>                      | 85                       |
| 7     | K-PPh <sub>2</sub>                       | 75                       |
| 8     | K-F                                      | 87                       |

[a] Yield of isolated product (average of two runs). [b] 95% purity.

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[+] X-ray crystal structure analysis.

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(Table 1, entries 4 and 5), amides and phosphides (Table 1, entries 6 and 7), as well as fluoride (Table 1, entry 8) all cleanly displace the triflate, presumably via an addition–elimination pathway. The syntheses illustrated in Table 1 and Scheme 2 describe the first examples of heteroatom-substituted 1,2-azaborolyls.

To gain insight into how the boron substituent affects the electronic nature of the iron, we have measured the oxidation potential of these new azaborolyl complexes (Table 2).<sup>[18]</sup> As expected, the NMe<sub>2</sub> and OMe groups are the best donors among those that we have examined (Table 2, entries 1 and 2). The *n*Bu, SBn, F, and allyl substituents appear to be modestly electron-donating (Table 2, entries 3–6) relative to H (Table 2, entry 7), whereas PPh<sub>2</sub> is electron-withdrawing (Table 2, entry 8).

Table 2. Oxidation potential of 1,2-azaborolyliron complexes as a function of the substituent on boron (0.0026 M; 0.10 M Bu<sub>4</sub>NPF<sub>6</sub>; CH<sub>2</sub>Cl<sub>2</sub>; 20 mV s<sup>−1</sup>; potentials relative to Ag/Ag<sup>+</sup> with  $E_{1/2} = 0.23$  V for Fc/Fc<sup>+</sup>).

| Entry | Boron substituent<br>Nu on <b>6</b> | $E_{pa}$ [V] <sup>[a]</sup> |
|-------|-------------------------------------|-----------------------------|
| 1     | NMe <sub>2</sub>                    | −0.26                       |
| 2     | OMe                                 | −0.08                       |
| 3     | <i>n</i> Bu                         | 0.07                        |
| 4     | SBn                                 | 0.08                        |
| 5     | F                                   | 0.08                        |
| 6     | allyl                               | 0.13                        |
| 7     | H                                   | 0.20                        |
| 8     | PPh <sub>2</sub>                    | 0.29                        |

[a]  $E_{pa}$  = anodic peak potential.

Using the data in Table 2 and a two-parameter Hammett analysis ( $\sigma_I$  = inductive component;  $\sigma_R$  = resonance component),<sup>[19, 20]</sup> we have determined an excellent correlation between observed and calculated oxidation potentials for these substituted 1,2-azaborolyl complexes (Figure 1;  $E_{pa} = 0.42\sigma_I + 0.94\sigma_R + 0.20$ ).

We have confirmed our structural assignment for azaborolyl complexes **6** through an X-ray crystallographic study of the *B*-OMe adduct (Figure 2). As expected on the basis of our electrochemical investigations, the OMe group adopts a

geometry consistent with  $\pi$  bonding between oxygen and boron (Figure 2).<sup>[21]</sup>

Finally, we have determined the impact that replacing two carbons of a cyclopentadienyl ligand with the corresponding isoelectronic B–N unit has on a metal. Thus, electrochemistry indicates that 1,2-azaborolyl is somewhat more electron-donating than cyclopentadienyl (Scheme 3).<sup>[22]</sup>

In summary, we have developed a synthetic route that provides access to a diverse array of the first *B*-heteroatom-substituted (H, N, O, F, P, S, and Cl) 1,2-azaborolyl complexes. In addition, we have established that the substituent on boron can modulate the reactivity of the complexes, specifically, their susceptibility to one-electron oxidation. Furthermore, we have determined

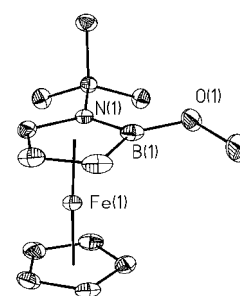
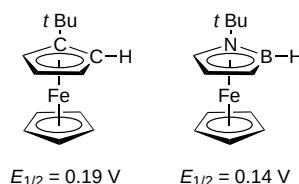


Figure 2. Molecular structure of azaborolyl complex **6** (Nu = OMe) (ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level).



Scheme 3. Direct electrochemical comparison between a 1,2-azaborolyl and a cyclopentadienyl complex (0.0026 M; 0.10 M Bu<sub>4</sub>NPF<sub>6</sub>; CH<sub>2</sub>Cl<sub>2</sub>; 20 mV s<sup>−1</sup>; potentials relative to Ag/Ag<sup>+</sup> with  $E_{1/2} = 0.23$  V for Fc/Fc<sup>+</sup>).

that a 1,2-azaborolyl is more electron-rich than an isostructural cyclopentadienyl ligand. In view of the ubiquity and the utility of cyclopentadienyl–metal complexes, we anticipate that the observations described in this study will stimulate the development of applications of  $\eta^5$ -(1,2-azaborolyl) ligands in metal-catalyzed processes.

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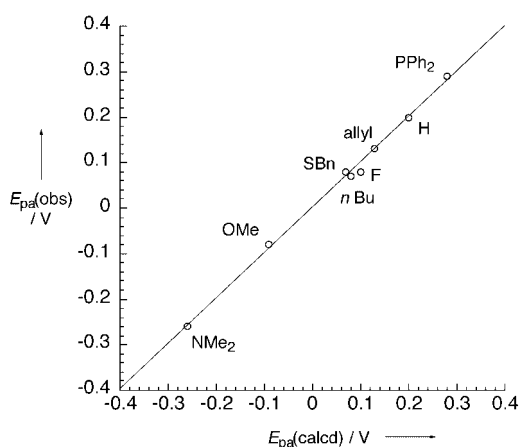


Figure 1. Observed and calculated (by Hammett analysis) oxidation potentials for substituted 1,2-azaborolyl complexes ( $E_{pa}(\text{calcd}) = 0.42\sigma_I + 0.94\sigma_R + 0.20$ ).

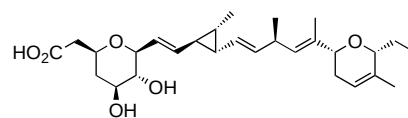
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## Total Synthesis of Ambruticin\*\*

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Ambruticin (**1**) was isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum* var. *fulvum*. It is an orally active antifungal agent showing in vitro and in vivo activity against a variety of pathogenic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*, as well as the dermatophytic filamentous fungi.<sup>[1]</sup> Ambruticin features unique *cis*-2,6-disubstituted tetrahydropyran and dihydropyran ring systems together with a methylcyclopropane moiety. In spite of considerable interest



**1** (+)-Ambruticin

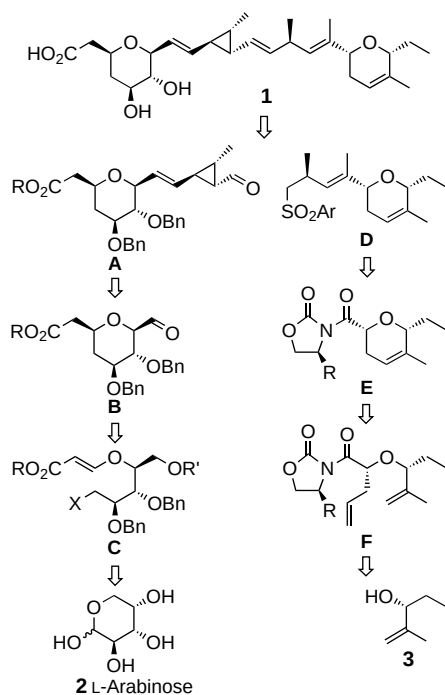
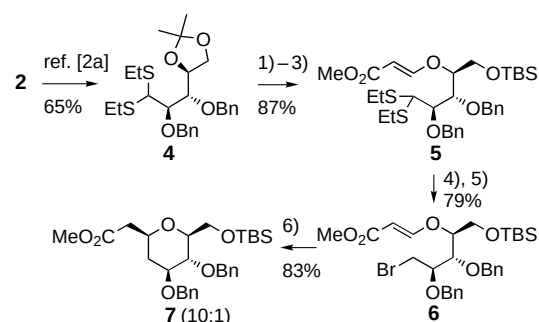
in the preparation of **1**,<sup>[2]</sup> we found in the literature only one total synthesis, reported by Kende in 1990,<sup>[3]</sup> and the difficulty in designing a stereoselective total synthesis is manifested in recent reports dealing with partial syntheses of the molecule.<sup>[4]</sup> In our continuing search for new applications of stereoselective radical cyclization reactions of  $\beta$ -alkoxyacrylates,<sup>[5]</sup> we examined the efficacy of these reactions in a stereocontrolled synthesis of **1**.

In our retrosynthetic analysis, the tetrahydropyran aldehyde **B** was to be prepared from a  $\beta$ -alkoxyacrylate precursor **C**, which may be obtained from *L*-arabinose (**2**). The dihydropyran derivative **E** was envisaged to arise from the diene **F** by olefin metathesis.<sup>[6]</sup> Connection of the parts **A** and **D** by Julia-type olefination would then complete the construction of the carbon framework (Scheme 1).

Selective acetonide protection of the dithioacetal derivative of *L*-arabinose (**2**) and benzylation of the remaining hydroxy groups gave the acetonide **4** (Scheme 2).<sup>[2a]</sup> The  $\beta$ -alkoxyacrylate **5** was obtained from **4** by acetonide deprotection, regioselective TBS protection of the primary hydroxy group, and reaction with methyl propiolate. The aldehyde group generated from the dithioacetal moiety in **5** was reduced with  $\text{NaBH}_4$ , and bromide substitution led to the primary bromide **6**, which was then stereoselectively transformed into the

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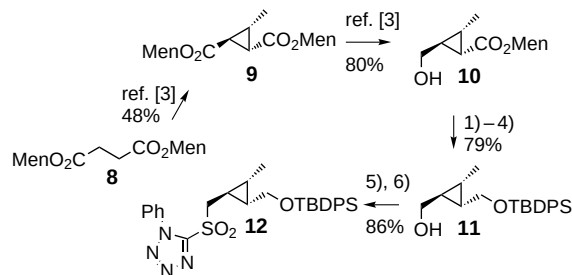
[\*\*] The authors thank the Ministry of Science and Technology, Republic of Korea, and Korea Institute of Science and Technology Evaluation and Planning for a National Research Laboratory grant (1999). The authors also thank Professor A. S. Kende (University of Rochester) for NMR spectra of natural and synthetic ambruticin, and Professor G. Höfle (GBF) for a sample of natural ambruticin and NMR spectra.


 Scheme 1. Retrosynthetic analysis of **1**.


Scheme 2. 1) Cat. HCl, MeOH, 0 °C → RT, 8 h. 2) 1.05 equiv TBSCl, 2.0 equiv imidazole, CH<sub>2</sub>Cl<sub>2</sub>, RT, 10 min. 3) 1.1 equiv HC≡CCO<sub>2</sub>Me, 0.2 equiv NMM, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h. 4) 1.5 equiv PhI(TFA)<sub>2</sub>, 3.0 equiv NaHCO<sub>3</sub>, MeCN/H<sub>2</sub>O (9:1), 0 °C, 5 min; 1.0 equiv NaBH<sub>4</sub>, 0 °C, 30 min. 5) 1.5 equiv CBr<sub>4</sub>, 1.2 equiv Ph<sub>3</sub>P, 3.0 equiv NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → RT, 2 h. 6) 1.2 equiv Bu<sub>3</sub>SnH, 0.2 equiv AIBN, benzene (0.005 M), reflux, 2 h, (syringe pump, 1 h). AIBN = azobisisobutyronitrile, NMM = *N*-methylmorpholine, TBS = *tert*-butyldimethylsilyl.

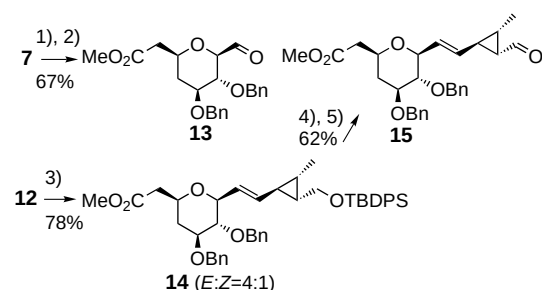
desired tetrahydropyran derivative **7** (2,6-*cis:trans* = 10:1) under the standard high-dilution radical-generating conditions in the presence of tributylstannane and AIBN.

Preparation of the primary alcohol **10** from dimethyl succinate (**8**) was achieved by following the Kende protocol,<sup>[3]</sup> which involves stereoselective double alkylation with 1-bromo-1-chloroethane, selective hydrolysis of the sterically less hindered ester moiety of the diester **9**, and borane reduction (Scheme 3). Conversion of **10** into the TBDPS ether **11** was then effected by TBS protection, LiAlH<sub>4</sub> reduction, TBDPS protection, and TBS deprotection. Mitsunobu-type reaction of **11** with 1-phenyl-1*H*-tetrazole-5-thiol proceeded efficiently to provide the expected sulfide, which was converted into the sulfone **12** by oxidation with MCPBA.



Scheme 3. 1) 1.1 equiv TBSCl, 2.0 equiv imidazole, CH<sub>2</sub>Cl<sub>2</sub>, RT, 30 min. 2) 1.5 equiv LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0 °C, 1 h. 3) 1.1 equiv TBDPSCl, 2.0 equiv imidazole, CH<sub>2</sub>Cl<sub>2</sub>, RT, 1 h. 4) 0.1 equiv CSA, MeOH, 0 °C, 40 min. 5) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph<sub>3</sub>P, THF, 0 °C, 5 min. 6) 2.0 equiv MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min. DIAD = diisopropyl azodicarboxylate, MCPBA = *m*-chloroperbenzoic acid, Men = menthyl, TBDPS = *tert*-butyldiphenylsilyl.

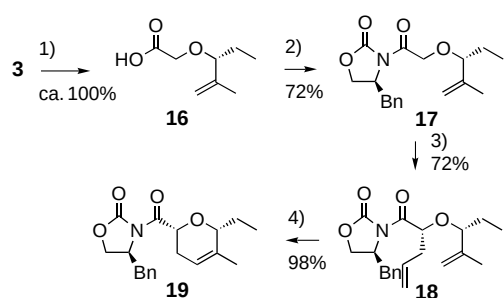
The aldehyde **13** was obtained from the TBS ether **7** by deprotection, separation of diastereomers, and Swern oxidation (Scheme 4). Construction of the *trans*-disubstituted double bond at C8–C9 was problematic. Classical Julia



Scheme 4. 1) Cat. HCl, MeOH, 0 °C → RT, 30 min. 2) 2.2 equiv (COCl)<sub>2</sub>, 4.0 equiv DMSO, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1 h; 5.0 equiv NEt<sub>3</sub>, –78 °C, 7 h. 3) 2.0 equiv NaHDMS, THF/HMPA (4:1), –78 °C, 5 min; 2.0 equiv **13**, –78 °C → RT, 3 h. 4) Cat. HCl, MeOH, RT, 1 h. 5) 2.2 equiv (COCl)<sub>2</sub>, 4.0 equiv DMSO, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 30 min; 5.0 equiv NEt<sub>3</sub>, –78 °C → RT. HMPA = hexamethylphosphoramide, NaHDMS = sodium hexamethyldisilazide.

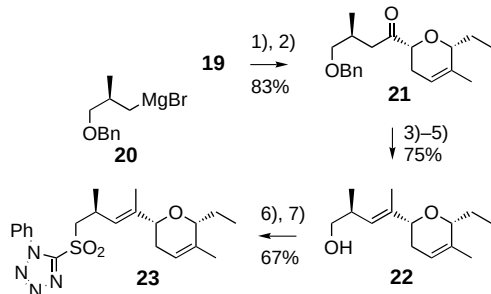
reactions employing the aldehyde **13** did not work, but after considerable experimentation, the Kocienski–Julia reaction proved fruitful.<sup>[7]</sup> The olefin **14** (*E:Z* = 4:1) was obtained in 78% yield by deprotonation of the sulfone **12** by two equivalents of sodium hexamethyldisilazide and subsequent addition of two equivalents of the aldehyde **13** in the presence of HMPA. Use of lithium hexamethyldisilazide gave **14** with better selectivity (*E:Z* = 9:1) but lower yield (63%), and the reaction became essentially nonstereoselective when potassium hexamethyldisilazide was employed (63% yield, *E:Z* = 1:1). The required aldehyde **15** was prepared from **14** by deprotection of the TBDPS group under acidic conditions, separation of the geometric isomers, and Swern oxidation.

Synthesis of the right-hand half of ambruticin (**1**) commenced with (*R*)-3-hydroxy-2-methylpent-1-ene (**3**),<sup>[8]</sup> which was converted to the ether **16** by reaction with sodium bromoacetate (Scheme 5). The sodium enolate of the corresponding imide **17** reacted with allyl iodide to yield the diene **18** in a stereoselective manner. Olefin metathesis of the diene **18** proceeded uneventfully with the Grubbs catalyst<sup>[9]</sup> to give the dihydropyran imide **19** in excellent yield.



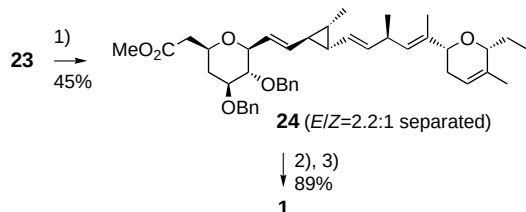
Scheme 5. 1) 1.0 equiv NaH, BrCH<sub>2</sub>CO<sub>2</sub>Na, RT, 8 h (reverse addition). 2) 1.0 equiv PivCl, 1.1 equiv NEt<sub>3</sub>, Et<sub>2</sub>O, −78 → 0 °C; 1.0 equiv X<sub>c</sub>-Li, THF, −78 °C, 8 h. 3) 1.2 equiv NaHDS, 5.0 equiv H<sub>2</sub>CCHCH<sub>2</sub>I, THF, −78 → −45 °C, 5 h. 4) 0.05 equiv [RhCl<sub>2</sub>(CHPh)(PCy<sub>3</sub>)<sub>2</sub>], CH<sub>2</sub>Cl<sub>2</sub> (0.005 M), reflux, 3 h; 0.075 equiv Pb(OAc)<sub>4</sub>. Piv = pivaloyl.

Conversion of **19** to the corresponding Weinreb amide and subsequent reaction with the Grignard reagent **20**<sup>[10]</sup> led to the ketone **21** (Scheme 6). The trisubstituted olefin **22** was obtained by regioselective enol triflate formation and reaction with lithium dimethylcuprate<sup>[11]</sup> followed by lithium/ammonia debenzoylation. Mitsunobu-type reaction of **22** with 1-phenyl-1*H*-tetrazole-5-thiol and selective oxidation with ammonium heptamolybdate and hydrogen peroxide<sup>[12]</sup> provided the sulfone **23** in reasonable yield.



Scheme 6. 1) 3.5 equiv MeNH(OMe)·HCl, 3.5 equiv Me<sub>3</sub>Al, THF, 0 °C, 3 h. 2) 3.0 equiv **20**, 40 °C, THF, 8 h. 3) 1.25 equiv LiHMDS, 1.5 equiv PhNTf<sub>2</sub>, THF/HMPA (4:1), −78 °C, 30 min. 4) 3.0 equiv Me<sub>2</sub>CuLi, Et<sub>2</sub>O, −78 °C, 1 h. 5) 10 equiv Li (×3), NH<sub>3</sub>(l)/EtOH (5:1), −78 °C, 10 min. 6) 2.0 equiv 1-phenyl-1*H*-tetrazole-5-thiol, 1.8 equiv DIAD, 1.5 equiv Ph<sub>3</sub>P, THF, 0 °C, 30 min. 7) 2.0 equiv (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>, H<sub>2</sub>O<sub>2</sub>, EtOH, 0 °C, 3 h.

The final coupling reaction was performed by treating the sulfone **23** with sodium hexamethyldisilazide in the presence of HMPA, and then with 1.5 equivalents of the aldehyde **15** (Scheme 7). Thus, 45% of the desired (*E*)-olefin **24** was



Scheme 7. 1) 1.2 equiv NaHDS, THF/HMPA (4:1), −60 °C, 30 min; 1.5 equiv **15**, −60 → 0 °C, 3 h. 2) 0.5 N LiOH, THF/H<sub>2</sub>O (3:1), RT, 8 h. 3) 10 equiv Li (×3), NH<sub>3</sub>(l)/EtOH (5:1), −78 °C, 10 min.

obtained directly along with the (*Z*)-isomer, which was isolated in 21% yield. Use of potassium hexamethyldisilazide resulted in higher stereoselectivity (*E*:*Z* = 6:1), but the yield was low (15%). Ambruticin (**1**) was obtained from **24** by basic hydrolysis and lithium/ammonia debenzoylation.

In summary, oxacyclic building blocks were prepared by using highly stereoselective radical cyclization and olefin metathesis reactions. The convergent strategy featuring the Kocienski–Julia reaction may be easily adapted to the synthesis of ambruticin analogues for the evaluation of bioactivities.

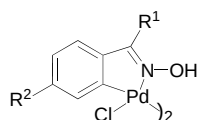
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# A Convenient Oxime-Carbapalladacycle-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides in Water\*\*

Luis Botella and Carmen Nájera\*

The importance of biaryl units<sup>[1]</sup> as components of many kinds of compounds, mainly pharmaceuticals, herbicides, and natural products, as well as in the field of engineering materials, such as conducting polymers, molecular wires, and liquid crystals, has attracted enormous interest from the chemistry community. Palladium- and nickel-catalyzed Suzuki–Miyaura cross-coupling<sup>[2]</sup> is the most important and efficient strategy for the construction of unsymmetrical biaryl compounds. This cross-coupling methodology allows the use of organic solvents and inorganic bases, tolerates many functional groups, is not affected by steric hindrance of the substrates, and is suitable for industrial processes.<sup>[3]</sup> From the industrial point of view, some important goals need to be realized for the development of this process: the functionalization of inexpensive and readily accessible aryl chlorides<sup>[4]</sup> and the use of water<sup>[5]</sup> as a safe and inexpensive solvent. Furthermore, to avoid an inert atmosphere, air-stable, efficient, and nontoxic catalysts are desired. The activation of both electron-deficient and electron-rich aryl chlorides has been achieved by palladium complexes in the presence of expensive and toxic phosphanes,<sup>[6]</sup> phosphites,<sup>[7]</sup> phosphane oxides,<sup>[8]</sup> palladium *N*-heterocyclic carbene complexes,<sup>[9]</sup> and palladium on carbon.<sup>[10]</sup> However, palladacycles<sup>[11]</sup> have only been used in the case of electron-deficient aryl chlorides.<sup>[12]</sup> Cross-coupling reactions with organoboranes are carried out in a mixture of an organic solvent and an aqueous inorganic base, generally under an inert atmosphere. In neat water, only sodium tetraphenylborate has been employed in the case of aryl chlorides, with PdCl<sub>2</sub> (3 mol %) as catalyst.<sup>[13]</sup> Herein we describe that oxime-derived palladacycles<sup>[14]</sup> are air- and



- 1a**; R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H  
**1b**; R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = OH  
**1c**; R<sup>1</sup> = *p*-HOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = OH

water-stable catalysts that are suitable for cross-coupling different aryl and heteroaryl chlorides with boronic acids in neat water. Different palladacycles and palladium salts were initially tested as possible candidates to study their catalytic activity on a model coupling reaction between phenylboronic acid and *p*-chloroacetophenone (Table 1). New oxime palladacycles **1b** and **1c** with hydroxy substituents on the aromatic ring were prepared by palladation with lithium tetrachloropalladate, as described for **1a**.<sup>[15]</sup> We have established the most efficient reaction conditions: palladium catalyst (0.01 mol %), K<sub>2</sub>CO<sub>3</sub>

base (2 equiv), and tetrabutylammonium bromide (TBAB, 0.5 equiv) in refluxing water (Method A). After 2 h, it was found that palladacycles **1** were very effective catalysts under these conditions, and gave high turnover numbers (TON; up to 7700) and turnover frequencies (TOF; up to 3850 h<sup>-1</sup>) (Table 1, entries 1–3), whereas no reaction or very low conversions were obtained with Li<sub>2</sub>PdCl<sub>4</sub> or Pd(OAc)<sub>2</sub>, respectively (Table 1, entries 4 and 5). For room temperature coupling reactions it was necessary to use methanol/water (3:1), higher catalyst loading (1 mol % of palladium), KOH base (2 equiv), and TBAB (1 equiv) (Method B). Under these conditions after 18 h, up to 50 % yield was observed with palladacycles **1**, whereas Pd(OAc)<sub>2</sub> gave less than 2 % yield (Table 1, entries 6–9).

Table 1. Reaction conditions and catalyst studies on the Suzuki coupling of *p*-chloroacetophenone and phenylboronic acid.

| $\text{CH}_3\text{CO}-\text{C}_6\text{H}_4-\text{Cl} + \text{C}_6\text{H}_5-\text{B}(\text{OH})_2 \xrightarrow[\text{Method A or B}]{\text{Pd}^{\text{II}}} \text{CH}_3\text{CO}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$ |                       |                                          |              |                          |      |                     |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|--------------|--------------------------|------|---------------------|--|
| Entry                                                                                                                                                                                                                       | Method <sup>[a]</sup> | Catalyst (mol % Pd)                      | <i>t</i> (h) | Yield (%) <sup>[b]</sup> | TON  | TOF h <sup>-1</sup> |  |
| 1                                                                                                                                                                                                                           | A                     | <b>1a</b> (0.01)                         | 2            | 69                       | 6900 | 3450                |  |
| 2                                                                                                                                                                                                                           | A                     | <b>1b</b> (0.01)                         | 2            | 77                       | 7700 | 3850                |  |
| 3                                                                                                                                                                                                                           | A                     | <b>1c</b> (0.01)                         | 2            | 69                       | 6900 | 3450                |  |
| 4                                                                                                                                                                                                                           | A                     | Li <sub>2</sub> PdCl <sub>4</sub> (0.01) | 2            | –                        | –    | –                   |  |
| 5                                                                                                                                                                                                                           | A                     | Pd(OAc) <sub>2</sub> (0.01)              | 2            | 5                        | 500  | 250                 |  |
| 6                                                                                                                                                                                                                           | B                     | <b>1a</b> (1)                            | 18           | 43                       | 43   | 2.4                 |  |
| 7                                                                                                                                                                                                                           | B                     | <b>1b</b> (1)                            | 18           | 50                       | 50   | 2.8                 |  |
| 8                                                                                                                                                                                                                           | B                     | <b>1c</b> (1)                            | 18           | 42                       | 42   | 2.3                 |  |
| 9                                                                                                                                                                                                                           | B                     | Pd(OAc) <sub>2</sub> (1)                 | 18           | 1.5                      | 1.5  | 0.008               |  |

[a] Method A: *p*-chloroacetophenone (2 mmol), PhB(OH)<sub>2</sub> (3 mmol), K<sub>2</sub>CO<sub>3</sub> (4 mmol), TBAB (1 mmol), water (7 mL), 100 °C; Method B: *p*-chloroacetophenone (2 mmol), PhB(OH)<sub>2</sub> (3 mmol), KOH (4 mmol), TBAB (2 mmol), methanol/water (3:1, 8 mL), room temperature. [b] Determined by means of GC, based on the aryl chloride.

In both methods, the presence of TBAB<sup>[16, 17]</sup> was crucial to enhance the rate of the coupling, presumably because of the formation of PhB(OH)<sub>3</sub><sup>-</sup>Bu<sub>4</sub>N<sup>+</sup>.<sup>[18]</sup> The catalyst **1b** was deactivated after the third cycle, when the coupling in water (Method A) was carried out in 1-h intervals (0.1 mol % catalyst): 99 % (first and second cycle), 75 % (third cycle), and 46 % (fourth cycle).

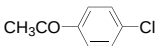
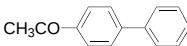
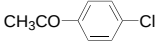
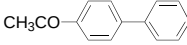
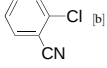
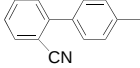
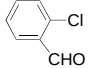
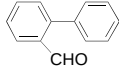
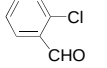
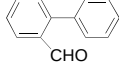
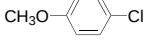
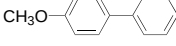
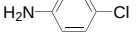
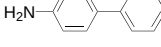
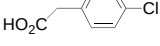
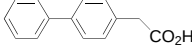
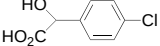
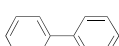
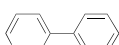
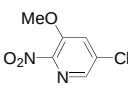
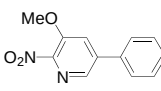
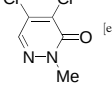
The cross-coupling reactions with different aryl and heteroaromatic chlorides were studied with complex **1b** as catalyst (Table 2, Method A). For the synthesis of 4'-methylbiphenyl-2-carbonitrile, an intermediate in the preparation of angiotensin II receptor antagonists such as DuP753 and other antihypertensive drugs, 2-chlorobenzonitrile was coupled with *p*-tolylboronic acid (Table 2, entry 3).

For less reactive aryl chlorides, the catalyst loading and the amount of TBAB was increased to accelerate the reactions (Table 2, entries 4–9, 12, and 13). Biaryl/acetic acids have applications in the pharmaceutical industry as well as in materials science<sup>[21]</sup> and have been prepared recently by means of a Suzuki reaction on a multigram scale by using Pd/C (3 mol %) in refluxing isopropyl alcohol/water for four days.<sup>[22]</sup> Similar reaction conditions were employed for the synthesis of *p*-aryl mandelic acids.<sup>[23]</sup> We found that biphenylacetic acid and *p*-phenylmandelic acid could be prepared for

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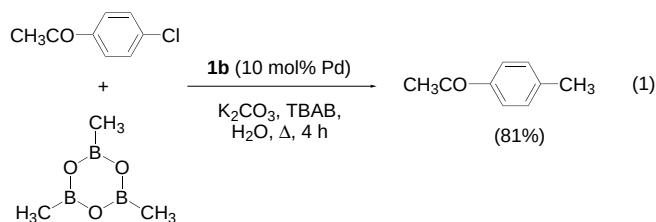
Table 2. Suzuki coupling of aryl chlorides and aryl boronic acids in water with **1b** as catalyst.

| Entry | ArCl                                                                                | mol % Pd         | TBAB(equiv) | <i>t</i> | Product                                                                               | Yield (%) <sup>[a]</sup> |
|-------|-------------------------------------------------------------------------------------|------------------|-------------|----------|---------------------------------------------------------------------------------------|--------------------------|
| 1     |    | 0.1              | 0.5         | 1 h      |    | 100 (98)                 |
| 2     |    | 0.01             | 0.5         | 2.5 h    |    | 91                       |
| 3     |    | 0.1              | 0.5         | 2 d      |    | 69                       |
| 4     |    | 1                | 1           | 2 h      |    | 27                       |
| 5     |    | 1 <sup>[c]</sup> | 1           | 32 h     |    | 57                       |
| 6     |    | 1                | 1           | 6 h      |    | 40                       |
| 7     |    | 1                | 1           | 6 h      |    | 83                       |
| 8     |    | 1                | 1           | 2.5 h    |    | 50                       |
| 9     |    | 1                | 1           | 2.5 h    |    | 42 <sup>[d]</sup>        |
| 10    |   | 1                | 0.5         | 3 h      |   | 92                       |
| 11    |  | 0.1              | 0.5         | 3 h      |  | 60                       |
| 12    |  | 1                | 1           | 4 h      |  | 76 (43)                  |
| 13    |  | 0.1              | 1           | 1 h      |  | 100 (92)                 |

[a] Determined by means of GC, based on the aryl chloride; yields in parenthesis are those of purified products. [b] *p*-Methylphenylboronic acid was used. [c] Method B was used. [d] Determined by means of <sup>1</sup>H NMR spectroscopy. [e] PhB(OH)<sub>2</sub> (2 equiv) was used.

the first time from the corresponding chlorides instead of from the bromides in only 2.5 h in refluxing water (Table 2, entries 8 and 9). Heteroaryl chlorides, such as chloropyridines (Table 2, entries 10–12) and 2-methyl-4,5-dichloro-3(2*H*)pyridazinone<sup>[24]</sup> (Table 2, entry 13) were transformed efficiently into the corresponding biaryl compounds. These reaction conditions for the large-scale synthesis of pyridazinones, which exhibit agrochemical and pharmaceutical activities, are more convenient than the previously described syntheses, which use Pd(PPh<sub>3</sub>)<sub>4</sub> (3 mol %) in refluxing toluene under a N<sub>2</sub> atmosphere.<sup>[24]</sup>

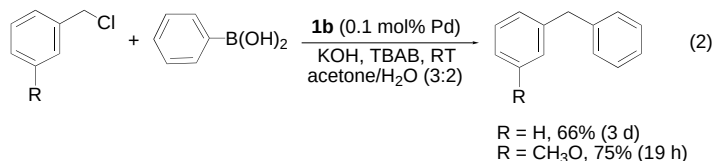
The cyclic anhydride trimethylboroxine (TMB) has been used recently for the Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed (10 mol %) methylation of electron-deficient aryl chlorides in refluxing aqueous dioxane (10 %) under nitrogen.<sup>[25]</sup> The use of TMB for the cross-coupling of 4-chloroacetophenone in refluxing water and with complex **1b** as catalyst (Method A) afforded 4-methylacetophenone in 81 % yield after 4 h [Eq. (1)].



The Suzuki Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed method has also been extended to the coupling of benzyl bromides and iodides with aryl boronic acids in refluxing EtOH/dimethoxyethane/water for 18 h under argon.<sup>[26]</sup> Oxime-derived palladacycle **1b** was an effective catalyst for the coupling of benzylic chlorides with phenylboronic acid. Benzyl chloride and 3-methoxybenzyl chloride reacted with phenylboronic acid at room temperature with low loading of catalyst (0.1 mol % Pd) to give diarylated methanes in 66 and 75 % yield, respectively



[Eq. (2)]. The best conditions for this reaction were similar to those for Method B: KOH as base and acetone/water (3:2) as solvent. When the reaction was carried out in refluxing water, considerable amounts of alcohols were formed.



In summary, we have found that different types of Suzuki–Miyaura couplings can be carried out in water in the presence of TBAB with activated and deactivated aryl or heteroaromatic chlorides as well as benzylic chlorides by means of stable and easily available oxime-derived palladacycles. Degassing of the solvent or inert atmosphere were unnecessary and other factors, such as the cost and stability of the catalyst and the water medium make this green methodology more useful than others recently described. All these features are very appropriate for industrial environmentally friendly processes. The accessibility and structural versatility of these palladacycles render very promising catalysts and further studies in the applicability of these systems in other organic transformations are currently under investigation.

#### Experimental Procedure

A solution of aryl chloride (2 mmol), PhB(OH)<sub>2</sub> (0.37 g, 3 mmol), K<sub>2</sub>CO<sub>3</sub> (0.55 g, 4 mmol), tetrabutylammonium bromide (0.64 g, 2 mmol), and compound **1b** (0.01 to 1 mol % Pd, see Tables 1 and 2) in water (7 mL) was heated at reflux. To measure the conversion of the reaction, a sample was taken from the cooled mixture and washed with H<sub>2</sub>O and EtOAc. Subsequently the cooled reaction mixture was extracted with EtOAc, the organic phase was dried and evaporated under vacuum, and the crude product was purified by recrystallization or by chromatography on silica gel.

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# Highly Efficient White Organic Electroluminescence from a Double-Layer Device Based on a Boron Hydroxyphenylpyridine Complex\*\*

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Organic electroluminescent (EL) devices are of growing interest in display applications because they can emit colors with high luminous efficiency throughout the visible spectrum. Extensive studies have been performed on the use of small molecular complexes to make organic EL devices with high brightness, multicolor emission, improved durability, and desirable efficiency.<sup>[1–16]</sup> While some applications require colored emission sources, others need a bright white-light source. Several methods of producing white light from polymer or small-molecule organic devices have been demonstrated.<sup>[17–21]</sup> To obtain white light efficiently with good color purity, complicated emitting material systems, multi-layer structures, and precise fabrication technologies were often necessary.<sup>[22, 23]</sup> A simple approach for making efficient white electroluminescent devices is urgently required. Recently, we found some hydroxyphenylpyridine complexes to be ideal emitting materials for EL devices.<sup>[24–27]</sup> Here we report on high-efficiency white electroluminescence from a double-layer device based on a luminescent boron complex of the dianion of 1,6-bis(2-hydroxy-5-methylphenyl)pyridine ((mdppy)BF).

The ligand 1,6-bis(2-hydroxy-5-methylphenyl)pyridine ( $H_2mdppy$ ) was prepared by the reaction of 2,6-dibromopyridine and the Grignard reagent from 2-bromo-4-methylanisole in THF with  $[NiCl_2(dppe)]$  as catalyst ( $dppe = Ph_2PCH_2CH_2PPh_2$ ). This was followed by demethylation in molten pyridinium chloride to give  $H_2mdppy$ . Reaction of  $H_2mdppy$  with one equivalent of  $BF_3$  in benzene gave (mdppy)BF.

The UV/Vis and photoluminescence (PL) spectra of (mdppy)BF in dichloromethane are displayed in Figure 1.

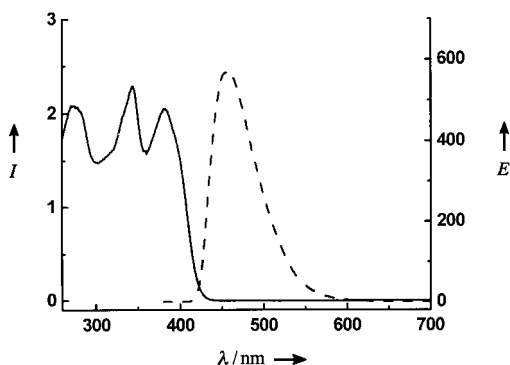


Figure 1. UV/Vis absorption (—) and emission (---) spectra of (mdppy)BF in dichloromethane.

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(mdppy)BF exhibits intensive blue luminescence in solution. The spectra of vacuum-evaporated films of  $N,N'$ -bis( $\alpha$ -naphthyl)- $N,N'$ -diphenyl-1,1'-biphenyl-4,4'-diamine (NPB) and (mdppy)BF are shown in Figure 2. The solid films of NPB and (mdppy)BF have similar photoluminescence properties,

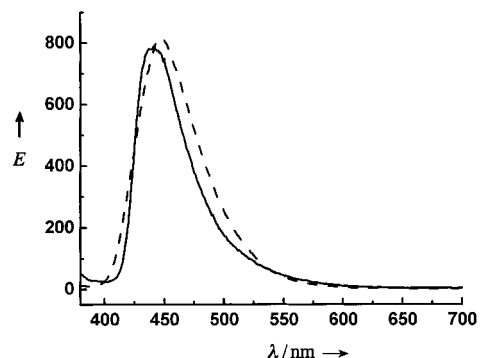


Figure 2. Photoluminescence spectra of solid thin films of (mdppy)BF (—) and NPB (---).

and they both emit blue light. To investigate the EL properties of (mdppy)BF, an organic electroluminescent device was fabricated by vacuum thermal evaporation of NPB and (mdppy)BF onto cleaned glass substrates precoated with conductive transparent indium tin oxide (ITO). The device consists of a 60 nm-thick layer of the hole-transporting material NPB, a 60 nm-thick layer of the emitting and electron-transporting material (mdppy)BF, a 1 nm-thick layer of LiF to enhance electron injection from aluminum, and a 200 nm-thick layer of aluminum metal. The device and the molecular structures of NPB and (mdppy)BF are presented in Figure 3. The device exhibited a significantly broader EL spectrum (Figure 4), ranging from 400 to 700 nm, which completely covers the total wavelength region of visible light emission, that is, high-quality white electroluminescence was obtained. The Commission Internationale de l'Eclairage (CIE) coordinates are (CIE; 0.30, 0.36); white is defined as (CIE; 0.33, 0.33). When the driving voltage was varied from 4 to 18 V, the CIE coordinates remained almost unchanged. The EL spectral component around 450 nm can be attributed to (mdppy)BF or NPB. The EL band beyond the blue region

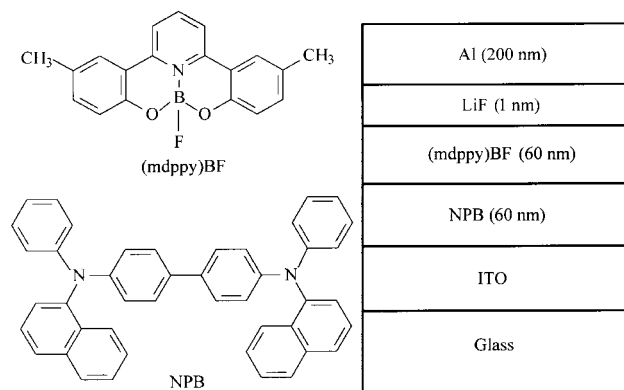


Figure 3. The EL device structure and molecular structures of (mdppy)BF and NPB.

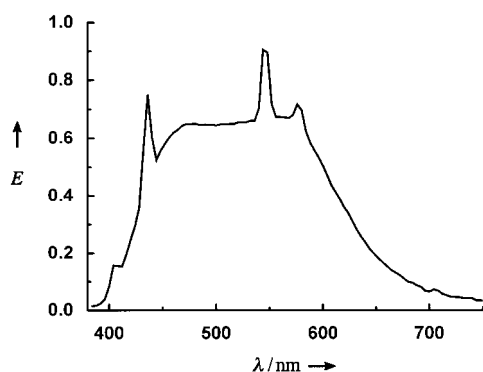


Figure 4. EL spectrum of the ITO/NPB/(mdppy)BF/LiF/Al device.

cannot be explained by singlet recombination in (mdppy)BF or NPB. We propose that this part of the EL band is due to exciplex emissions. The turn-on voltage of the device is 4.0 V and the maximum luminance is  $3500 \text{ cd m}^{-2}$  at a driving voltage of 18 V. The device showed a maximum EL efficiency of  $3.6 \text{ lm w}^{-1}$  ( $6.5 \text{ cd A}^{-1}$ ) with a luminance of  $110 \text{ cd m}^{-2}$  at a driving voltage of 5.5 V. To our knowledge, it is the highest efficiency for a white-light organic EL device that has been achieved until now. It reached an efficiency of  $1.5 \text{ lm w}^{-1}$  ( $3.3 \text{ cd A}^{-1}$ ) and a luminance of  $620 \text{ cd m}^{-2}$  at a current density of  $20 \text{ mA cm}^{-2}$  and a driving voltage of 7.0 V. Thus, the device exhibits high EL efficiency at higher luminances. Figure 5 presents the current–voltage and luminance–voltage characteristics of the device. We have not yet studied the

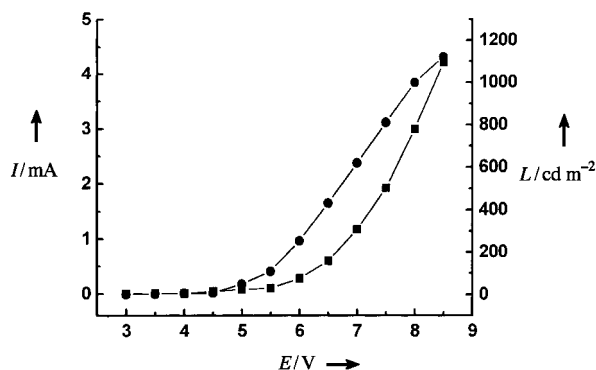


Figure 5. Current–voltage (■) and luminance–voltage (●) characteristics of the ITO/NPB/(mdppy)BF/LiF/Al device.

lifetime of the device yet, but the unencapsulated device was stable, and the emission color did not change during the measurements of the EL spectrum, the CIE coordinates, and the luminance–voltage and current–voltage characteristics.

To investigate the exciplex emission properties of the NPB/(mdppy)BF system, a series of evaporated-film samples (Figure 6) were prepared on quartz substrates, and their PL spectra were recorded. The film samples consisted of a layer of NPB, a layer of (mdppy)BF, and an intermediate codeposited layer of NPB:(mdppy)BF (ca. 1:1 w/w). The thickness of the codeposited layer was varied from 0 to 120 nm. The total thickness of each film sample was 120 nm. The double-layer sample without a codeposited layer and the single-layer sample with only the codeposited layer represent the two

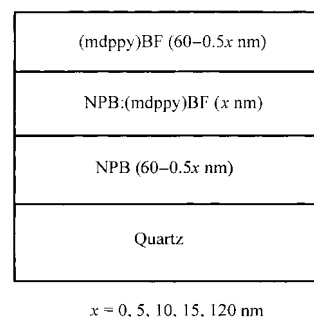


Figure 6. Schematic presentation of the film samples for PL measurements.

extremes. Figure 7 presents the PL spectra of the film samples. The exciplex emissions beyond the blue region grew with increasing thickness of the codeposited layer. It can be concluded that the interaction between NPB and (mdppy)BF molecules results in exciplex emission. The single-layer film sample exhibits a significantly broader PL spectrum that ranges from 400 to 650 nm.

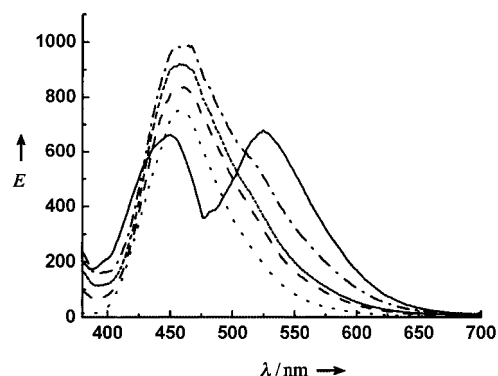


Figure 7. The PL spectra of film samples with structure NPB(60–0.5x nm)/NPB:(mdppy)BF(x nm)/(mdppy)BF(60–0.5x nm):  $x = 0 \text{ nm}$  (—);  $x = 5 \text{ nm}$  (---);  $x = 10 \text{ nm}$  (....);  $x = 15 \text{ nm}$  (—•—).

In the photoluminescence of an organic multilayer film, excitons are generated both in the bulk of each layer and at the interfaces. In a multilayer film without a blended layer, the PL properties are mainly determined by the bulk material, because the ratio of interface to bulk materials is small. In a multilayer film, the excitons that result from carrier injection and recombination are produced within a narrow interface region,<sup>[2]</sup> and the EL properties of the multilayer film are mainly determined by the interfacial characteristics. For a double-layer NPB/(mdppy)BF film, the electroluminescence is confined to the interfacial region and hence exhibits stronger exciplex emission characteristics than photoluminescence. Therefore, it is reasonable that the EL spectrum of the double-layer NPB:(mdppy)BF film is similar to the PL spectrum of the single-layer codeposited NPB:(mdppy)BF film, in which the ratio of interface to bulk of two materials is very high. The PL spectrum of the single-layer NPB:(mdppy)BF film and the EL spectrum of double-layer NPB/(mdppy)BF film have different line shapes. This may be because electron injection can sometimes generate excitons

that cannot be induced by optical excitation.<sup>[20]</sup> Furthermore, the refractive, reflective, and absorptive properties of ITO and the metal cathode also can affect the EL spectrum.<sup>[21]</sup>

In summary, the new luminescent material (mdppy)BF was synthesized and its electroluminescent properties were investigated. Highly efficient white-light EL devices can be fabricated from this material. The white electroluminescence is caused by exciplex emissions at the interface between NPB and (mdppy)BF. This offers the opportunity for constructing high-performance white EL devices based on only one emitting material and with a simple device structure. In addition, the EL device reported here may have potential applications in microcavity EL devices for selectively enhancing individual or multiple colors that lie within the EL spectrum band.<sup>[28]</sup>

## Experimental Section

**Synthesis of H<sub>2</sub>mdppy:** A solution of the Grignard reagent prepared from 2-bromo-4-methylanisole (6.0 g, 30 mmol) was added dropwise to an ice-cold mixture of [NiCl<sub>2</sub>(dppe)] (0.52 g, 1 mmol) and 2,6-dibromopyridine (3.6 g, 15 mmol) in anhydrous THF (40 mL) under nitrogen. The mixture was stirred at room temperature for 12 h and then quenched with aqueous NH<sub>4</sub>Cl. THF was removed under reduced pressure. The resulting white precipitate was filtered off, washed with water, and dried in air to give 1,6-bis(2-methoxy-5-methylphenyl)pyridine, which was used directly in the subsequent step without further purification. 1,6-bis(2-methoxy-5-methylphenyl)pyridine was added to molten pyridinium chloride (from 40 mL pyridine and 45 mL concentrated HCl) under nitrogen over 3 h at 200 °C. After addition of water to the mixture and neutralization with aqueous KOH, the crude product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 60 mL). The organic phase was washed with water (2 × 30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure. The residual yellow solid was purified by chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>) to give the product as a white powder in 55 % yield. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.00 (t, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 1.6 Hz, 2H), 7.16 (dd, *J* = 8.3, 1.9 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 2.37 (s, 6H). MS: *m/z* (%): 291 (100) [*M*<sup>+</sup>]; elemental analysis (%) calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>2</sub>: C 78.35, H 5.84, N 4.81; found: C 77.88, H 5.65, N 4.52.

**Synthesis of (mdppy)BF:** BF<sub>3</sub>·OEt<sub>2</sub> (1.42 g, 10 mmol), H<sub>2</sub>mdppy (2.91 g, 10 mmol), and NEt<sub>3</sub> (1 mL) were dissolved in 30 mL of benzene, and the reaction mixture was heated to reflux for 10 h. A light yellow solid precipitated from the solution. The solid product (75 % yield) was collected by filtration and purified by recrystallization and sublimation. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.08 (t, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 1.2 Hz, 2H), 7.28 (dd, *J* = 8.4, 1.70 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.36 (s, 6H). MS: *m/z* (%): 319 (100) [*M*<sup>+</sup>]; elemental analysis (%) calcd for C<sub>19</sub>H<sub>15</sub>NO<sub>2</sub>BF: C 71.47, H 4.70, N 4.39; found: C 70.76, H 4.33, N 4.16.

**Fabrication of electroluminescent devices:** The device was built on glass which was precoated with ITO with a sheet resistance of 20 Ω cm<sup>-2</sup>. The ITO glass was routinely cleaned by ultrasonic treatment in detergent solutions, rinsed with acetone, boiled in isopropyl alcohol, rinsed with methanol, and then with de-ionized water. The glass was dried in a vacuum oven between each cleaning step. The devices were fabricated by successive vacuum deposition of organic materials onto the ITO-coated glass

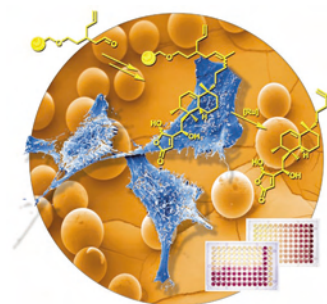
substrate. Prior to deposition, all organic materials were purified by sublimation. A shadow mask with 2 × 3 mm<sup>2</sup> openings was used to define the cathodes. The EL spectrum, luminance, and CIE coordinates of the device were recorded on a PR650 spectrometer. Luminance–voltage and current–voltage characteristics were measured at room temperature under ambient atmosphere.

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## COVER PICTURE

The cover picture shows schematically the 11-step synthesis of 6-*epi*-dysidiolide on a solid support. By means of this extraordinarily demanding and long solid-phase synthesis a small library of analogues of the Cdc25 protein phosphatase inhibitor dysidiolide was synthesized. This synthesis demonstrates that the solid-phase synthesis of natural products and compound libraries derived from them is feasible. This is a decisive cornerstone of a new principle for enhancing the efficiency of the hit- and lead-finding processes in pharmaceutical research based on natural products and their interaction with protein domains. Electron microscopy pictures of polymer beads and tumor cells are shown in the background. A 2-nm-thick gold layer was vaporized on to the resin beads. Tumor cells floating in front of the beads were employed in a cytotoxicity assay. The results of the assay are readily seen on the microtiter plates with the naked eye: living cells reduce a yellow tetrazolium salt to a red-violet dye. A detailed description of the study is reported by H. Waldmann et al. on p. 307 ff.

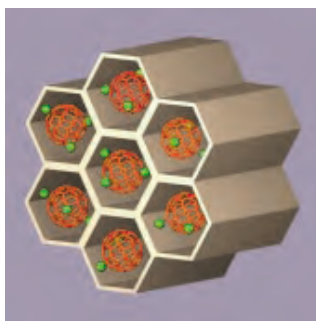


## REVIEWS

Contents

**Semiconductors, fuel cells, and stoichiometric electron acceptors** are just three of the applications of non-silica mesoporous materials which have novel electronic and electrooptical properties. The chemical composition of these materials is as varied as their chemistry and encompasses structures based on transition metal oxides, sulfides, and selenides, and the incorporation of alkali metal fullerenes and metallocenes. The picture shows a niobium oxide host with incorporated  $K_3C_{60}$  units which form a one-dimensional wire within the pores of the oxide framework.

*Angew. Chem.* **2002**, *114*, 222–238



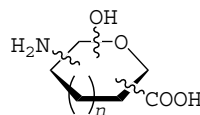
X. He, D. Antonelli\* ..... 214–229

Recent Advances in Synthesis and  
Applications of Transition Metal  
Containing Mesoporous Molecular Sieves

**Keywords:** electronic properties •  
mesoporous materials • semiconductors •  
solid-state structures • template synthesis



**Sugar–amino acid hybrids** combine the molecular features of amino acids and carbohydrates. These hybrids (see picture) are attractive building blocks and scaffolds for combinatorial synthesis because of their polyfunctional nature. Oligomerization and derivatization of these hybrids have resulted in novel glycomimetics, peptidomimetics, and biopolymers, many of which are biologically active.



*Angew. Chem.* **2002**, *114*, 240–264

F. Schweizer\* ..... 230–253

Glycosamino Acids: Building Blocks for Combinatorial Synthesis—Implications for Drug Discovery

**Keywords:** combinatorial chemistry • glycoconjugates • glycomimetics • peptidomimetics • sugar amino acids

## ESSAY

**Alzheimer's disease, type II diabetes, Creutzfeldt–Jakob disease, and amyloid-related diseases:** In each of these pathological situations, well-folded proteins undergo an irreversible transition from the “correctly folded” state to a collapsed  $\beta$ -sheet-rich structure. Here it is suggested that the aggregated form represents a global minimum in Gibbs energy for ensembles of protein molecules in general, and that at an infinite time *any* protein solution above a critical concentration will eventually undergo structural transition into the aggregated state.

*Angew. Chem.* **2002**, *114*, 267–269

E. Gazit\* ..... 257–259

The “Correctly Folded” State of Proteins: Is It a Metastable State?

**Keywords:** aggregation • amyloidosis • protein folding • proteins

## VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.com>

Gold–Xenon Complexes

T. Drews, S. Seidel, K. Seppelt\* ◆

Iron-Catalyzed Polyethylene Chain Growth on Zinc: Linear  $\alpha$ -Olefins with a Poisson Distribution

G. J. P. Britovsek, S. A. Cohen, V. C. Gibson,\* P. J. Maddox, M. van Meurs\* ◆

The Uronium/Guanidinium Peptide Reagents: Finally the True Uronium Salts

L. A. Carpino,\* H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mügge, H. Wenschuh, J. Klose, M. Beyermann, M. Bienert ◆

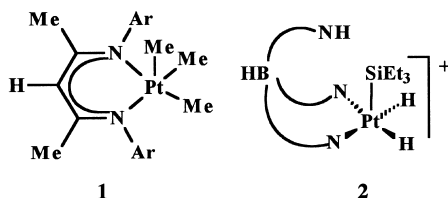
Nonrelaxable Anisotropic Organization of Organic-Inorganic Hybrid Materials Induced by an Electric Field

G. Cerveau, R. J. P. Corriu,\* E. Framery, S. Ghosh, M. Nobili

A Nanoporous Metal-Organic Framework Based on Bulky Phosphane Ligands

X. Xu, M. Nieuwenhuyzen, S. L. James\*

**A breakthrough in understanding hydrocarbon activation by platinum complexes** has been achieved by two research groups who report the isolation of model compounds **1** and **2** for the proposed unsaturated platinum(IV) complex intermediates.



R. J. Puddephatt\* ..... 261–263

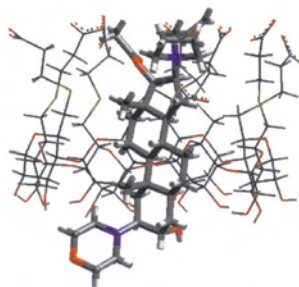
Coordinative Unsaturation in Platinum(IV) Chemistry: From Proposed Reaction Intermediates to the First Structurally Characterized Complexes

**Keywords:** C–C activation • C–H activation • coordination chemistry • homogeneous catalysts • platinum

*Angew. Chem.* **2002**, *114*, 271–273

## COMMUNICATIONS

**Superior to current clinically used reversal agents** in terms of efficacy and side effects: The formation of a high-affinity host–guest binary complex (association constant  $K_a$ : ca.  $10^7 \text{ M}^{-1}$ ) between the aminosteroidal guest molecule rocuronium bromide, the most widely used neuromuscular blocking agent in surgery, and a cyclodextrin-based synthetic host molecule (see X-ray crystal structure) results in reversal of the neuromuscular blockade induced by rocuronium bromide.



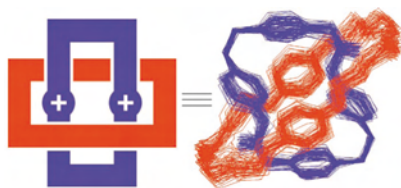
A. Bom, M. Bradley, K. Cameron, J. K. Clark, J. van Egmond, H. Feilden, E. J. MacLean, A. W. Muir, R. Palin, D. C. Rees, M.-Q. Zhang\* .... 265–270

A Novel Concept of Reversing Neuromuscular Block: Chemical Encapsulation of Rocuronium Bromide by a Cyclodextrin-Based Synthetic Host

**Keywords:** cyclodextrins • drug design • host–guest systems • medicinal chemistry • neuromuscular blockers

*Angew. Chem.* **2002**, *114*, 276–280

**A dicationic macrocycle** containing two  $\text{NH}_2^+$  centers can insert itself spontaneously inside bisparaphenylene[34]crown-10 to form a highly ordered, stable, 1:1 complex in solution, as well as in the solid state (see picture). The self-assembly of this superstructure, wherein the mean planes of the two macrocycles are aligned approximately orthogonally to one another, augurs well for the use of supramolecular assistance to covalent synthesis in the construction of interlocked molecular compounds beyond catenanes and rotaxanes.



S.-H. Chiu, A. R. Pease, J. F. Stoddart,\* A. J. P. White, D. J. Williams\* . 270–274

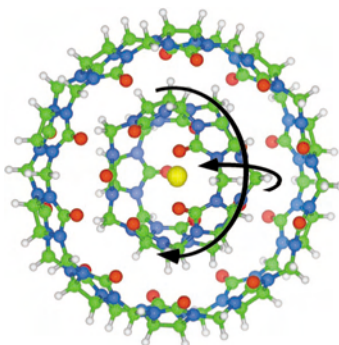
A Ring-in-Ring Complex

**Keywords:** crown compounds • hydrogen bonding • molecular recognition • self-assembly

*Angew. Chem.* **2002**, *114*, 280–284



**Concentric rotating and precessing macrocycles:** The crystal structure of the inclusion complex of cucurbit[5]uril within cucurbit[10]uril shows the macrocycles to be concentric but not coaxial, and with a chloride ion at the center (see structure). Both rings rotate freely relative to each other in solution, as shown by NMR spectroscopy. The facile axial and precessive motion of the inner ring relative to the outer ring represents the molecular analogy of the gyroscope.



A. Day,\* R. J. Blanch,\* A. P. Arnold, S. Lorenzo, G. R. Lewis, I. Dance ..... 275–277

A Cucurbituril-Based Gyroscane: A New Supramolecular Form

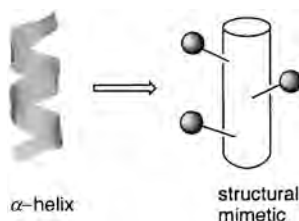
**Keywords:** host–guest systems • molecular machines • nanostructures • self-assembly • supramolecular chemistry

*Angew. Chem.* **2002**, *114*, 285–287





**Low micromolar inhibition of HIV-1 fusion** into host cells has been achieved by using a small molecule antagonist for the disruption of the gp41 core that was designed by mimicry of the  $\alpha$ -helical 4-3 hydrophobic repeat regions (see schematic representation).



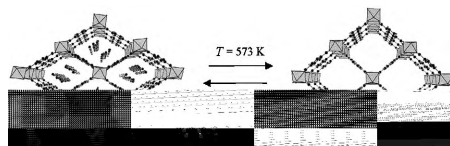
*Angew. Chem.* **2002**, *114*, 288–291

J. T. Ernst, O. Kutzki, A. K. Debnath,  
S. Jiang, H. Lu,  
A. D. Hamilton\* ..... 278–281

Design of a Protein Surface Antagonist  
Based on  $\alpha$ -Helix Mimicry: Inhibition of  
gp41 Assembly and Viral Fusion

**Keywords:** drug design • HIV • proteins •  
proteomimetics

**Breathtaking** are the highly magnetic and porous vanadocarboxylates ( $T_N = 95$  K) MIL-47as (left) and evacuated MIL-47 (right) that exhibit three-dimensional large-pore structures built up from infinite chains of corner-sharing  $V^{III}O_4(OH)_2$  (MIL-47as) and  $V^{IV}O_6$  (MIL-47) octahedra linked by rigid terephthalate anions. The reversible adsorption–desorption corresponds to a breathing of the structure. The high  $T_N$  value results from the combination of magnetic chains with the presence of the  $\pi$  electrons of the terephthalate.



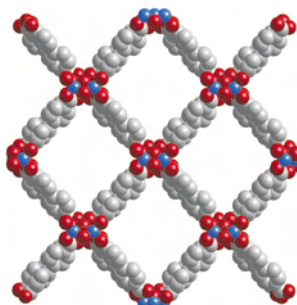
*Angew. Chem.* **2002**, *114*, 291–294

K. Barthelet, J. Marrot, D. Riou,\*  
G. Férey ..... 281–284

A Breathing Hybrid Organic–Inorganic  
Solid with Very Large Pores and High  
Magnetic Characteristics

**Keywords:** carboxylate ligands •  
magnetic properties • microporous  
materials • organic–inorganic hybrid  
composites • vanadium

**Interlinked Zn–O–C** infinite secondary building units (SBUs) form the basis of the novel metal-organic frameworks (MOFs)  $[Zn_3(OH_2)(X)_2] \cdot 4DEF \cdot 2H_2O$  (MOF-69A:  $X = 4,4'$ -biphenyldicarboxylate; MOF-69B:  $X = 2,6$ -naphthalenedicarboxylate;  $DEF = N,N'$ -diethylformamide). The nature of the infinite SBUs results in frameworks (structure of MOF-69A depicted) wherein catenation is forbidden.



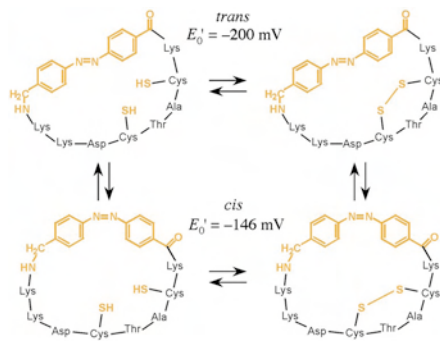
*Angew. Chem.* **2002**, *114*, 294–297

N. L. Rosi, M. Eddaoudi, J. Kim,  
M. O’Keeffe, O. M. Yaghi\* ... 284–287

Infinite Secondary Building Units and  
Forbidden Catenation in Metal-Organic  
Frameworks

**Keywords:** carboxylate ligands •  
copolymerization • interpenetration •  
secondary building units • zeolite  
analogues • zinc

**The conformational transition** of the disulfide-bridged bicyclic peptide (see picture) and of the related reduced monocyclic peptide induced by photoisomerization of the azobenzene moiety is responsible for significant differences in the redox properties. These can be exploited for photomodulation of rates and yields of in vitro oxidative folding of reduced and denatured RNase A as a model protein.



*Angew. Chem.* **2002**, *114*, 299–302

A. Cattani-Scholz, C. Renner, C. Cabrele,  
R. Behrendt, D. Oesterheld,  
L. Moroder\* ..... 289–292

Photoresponsive Cyclic  
Bis(cysteiny)lpeptides as Catalysts of  
Oxidative Protein Folding

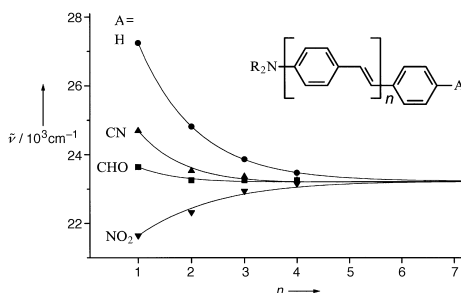
**Keywords:** azo compounds •  
conformation analysis • isomerization •  
peptides • redox chemistry



**Hypsochromic or bathochromic?**

Depending upon the acceptor group ( $A = \text{H}, \text{CN}, \text{CHO}, \text{NO}_2$ ) the position and intensity of the absorption maxima of a series of substituted oligo(phenylenevinylene)s change (see picture). Supported by semi-empirical calculations, the extent and direction of the shift (hypsochromic or bathochromic) is attributable to the opposing effects of length of conjugation and charge transfer.

*Angew. Chem.* **2002**, *114*, 302–306



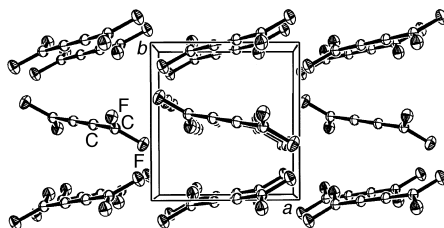
H. Meier,\* J. Gerold, H. Kolshorn,  
W. Baumann,\* M. Bletz ..... 292–295

Oligo(phenylenevinylene)s with Terminal  
Donor–Acceptor Substitution

**Keywords:** absorption • conjugation •  
donor–acceptor systems • oligomers •  
semiempirical calculations

**Despite its high instability**, the cumulene 1,1,4,4-tetrafluorobutatriene was obtained in a crystalline form. Its X-ray structure characterization revealed the presence of a herringbone motif in the solid state (see picture). Experimental and calculated charge density distributions show, as expected, that the central double bond is shorter and displays a higher charge density than the two outer double bonds.

*Angew. Chem.* **2002**, *114*, 311–314



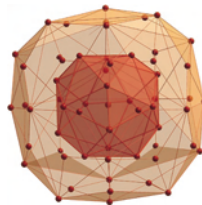
A. Bach, D. Lentz,\* P. Luger,\*  
M. Messerschmidt, C. Olesch,  
M. Patzschke ..... 296–299

Crystal Structure Analysis of 1,1,4,4-  
Tetrafluorobutadiene and Experimental  
Determination of the Charge Density of  
1,1,4,4-Tetrafluorobutatriene

**Keywords:** charge density • C–C  
coupling • cumulenes • solid-state  
structures • X-ray diffraction

**124 silver atoms and 57 selenido ligands** are contained in the cluster complex  $[\text{Ag}_{124}\text{Se}_{57}(\text{SePtBu}_2)_4\text{Cl}_6(\text{tBu}_2\text{P}(\text{CH}_2)_3\text{PtBu}_2)_{12}]$ . The molecule has an approximate diameter of 3 nm. The selenium substructure (see picture) is formed of spheres with a central Frank–Kasper polyhedron (red). Apart from this silver selenide cluster, three smaller silver–selenide cluster complexes are described.

*Angew. Chem.* **2002**, *114*, 306–310



D. Fenske,\* T. Langetepe ..... 300–304

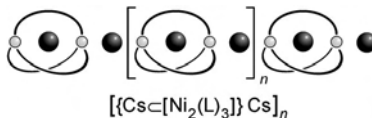
Synthesis and Structures of  
Silver–Selenide Cluster Complexes  
 $[\text{Ag}_4(\text{SePr})_4(\text{dppm})_2]$ ,  
 $[\text{Ag}_8(\text{SeEt})_8(\text{dppp})]_\infty$ ,  
 $[\text{Ag}_{28}\text{Se}_6(\text{SenBu})_{16}(\text{dppp})_4]$ , and  
 $[\text{Ag}_{124}\text{Se}_{57}(\text{SePtBu}_2)_4\text{Cl}_6(\text{tBu}_2\text{P}(\text{CH}_2)_3\text{PtBu}_2)_{12}]$

**Keywords:** cluster compounds •  
nanoparticles • selenium • silver •  
solid-state structures

**A molecular wagon train composed of self-complementary containers**

(shown schematically) results from the reaction of catecholate-spacer bis-1,3-diketones with nickel acetate in the presence of an excess of cesium ions. The most remarkable feature of this assembly is the oxo-bridged metal string running through it.

*Angew. Chem.* **2002**, *114*, 323–326

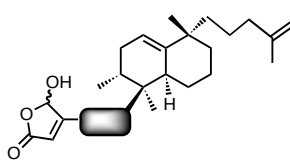


R. W. Saalfrank,\* H. Maid, N. Mooren,  
F. Hampel ..... 304–307

Hybrid Metallacoronates or One-  
Dimensional Oxo-Bridged Metal Strings  
by Self-Assembly—Coordination  
Number Controlled Product Formation

**Keywords:** copper • metallacryptates •  
nickel • oxo-bridged metal strings •  
self-assembly

**A multistep solid-phase synthesis** was used successfully to prepare a series of analogues (see picture) of the protein phosphatase inhibitor dysidiolide. The natural product and its analogues were prepared on a solid support over 8–12 linear steps with overall yields of 6–27 %. The analogues display pronounced antitumor activity in cell-based assays.



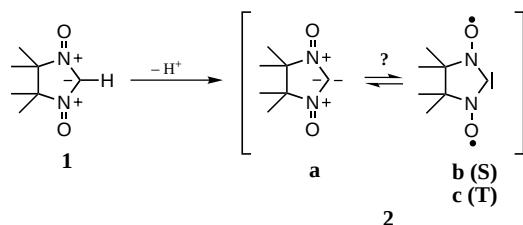
D. Brohm, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann\* ..... 307–311

Natural Products Are Biologically Validated Starting Points in Structural Space for Compound Library Development: Solid-Phase Synthesis of Dysidiolide-Derived Phosphatase Inhibitors

**Keywords:** combinatorial chemistry • natural products • proteins • solid-phase synthesis • total synthesis

*Angew. Chem.* **2002**, *114*, 319–323

**By deprotonation of the nitronylnitrosonium cation 1** the dinitroxide carbene **2** was prepared in solution (see scheme, S=singlet, T=triplet). Carbene **2** is the first example of a new class of carbenes with autoumpolung capability, the electronic structure of which is discussed in terms of configurations **2a–c**. Stable transition metal complexes derived from **2a** were synthesized and structurally characterized.



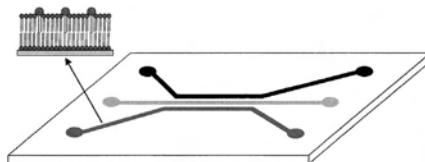
R. Weiss,\* N. Kraut ..... 311–314

Dinitroxide Carbenes, A New Class of Carbenes with Autoumpolung Character: Preparation in Solution and Stabilization in Transition Metal Complexes

**Keywords:** autoumpolung • carbene ligands • palladium • radicals

*Angew. Chem.* **2002**, *114*, 327–329

**Selectively functionalized micrometer-sized compartments** of solid-supported lipid bilayers (see schematic representation) were generated by a new procedure. These compartments are particularly suitable for carrying out optical and scanning force microscopy investigations of ligand–receptor interactions.



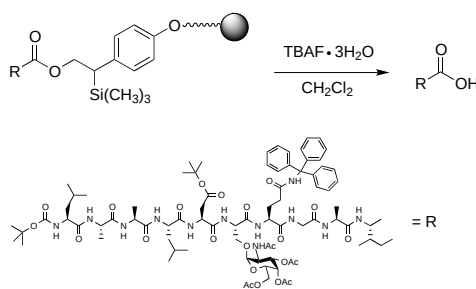
S. Künneke, A. Janshoff\* ..... 314–316

Visualization of Molecular Recognition Events on Microstructured Lipid-Membrane Compartments by In Situ Scanning Force Microscopy

**Keywords:** biosensors • lipids • molecular recognition • scanning probe microscopy • soft lithography

*Angew. Chem.* **2002**, *114*, 330–332

**Suitable for the immobilization of carboxylic acids**, the (2-phenyl-2-trimethylsilyl)ethyl linker was developed as a novel, fluoride-sensitive anchor. Cleavage with tetrabutylammonium fluoride (TBAF) trihydrate in  $\text{CH}_2\text{Cl}_2$  under almost neutral conditions gives the corresponding peptides and glycopeptides in high yields and purity without affecting aspartate structures and most of the common protecting groups in peptide chemistry (see scheme).



M. Wagner, H. Kunz\* ..... 317–321

The (2-Phenyl-2-trimethylsilyl)ethyl (PTMSEL) Linker—A Novel Linker for the Solid-Phase Synthesis of Protected Peptides and Glycopeptides Cleavable with Fluoride

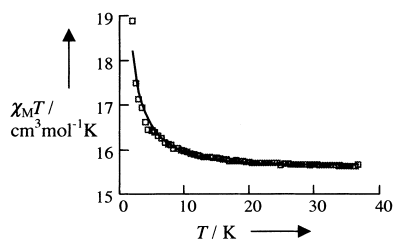
**Keywords:** glycopeptides • peptides • protecting groups • solid-phase synthesis

*Angew. Chem.* **2002**, *114*, 315–319



**An intramolecular ferromagnetic interaction** (see picture) is evidenced for the first time in a dinuclear gadolinium complex that has four carboxylate bridges. A similar interaction exists in a dinuclear erbium complex, but, as a result of the depopulation of the excited Stark levels, its signature only appears at very low temperature.

*Angew. Chem.* **2002**, *114*, 333–335



J.-P. Costes,\* J. M. Clemente-Juan,  
F. Dahan, F. Nicodème,  
M. Verelst ..... 323–325

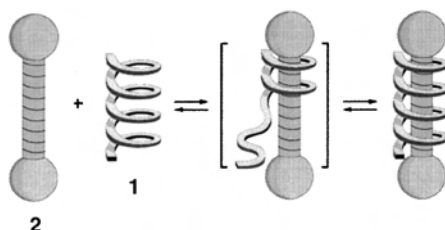
Unprecedented Ferromagnetic Interaction in Homobinuclear Erbium and Gadolinium Complexes: Structural and Magnetic Studies

**Keywords:** coordination chemistry • lanthanides • magnetic properties • rare-earth compounds



**A dynamic binding mechanism** allows the association of dumbbell-shaped ligand **2** with helical folded oligo(*m*-phenyleneethynylene)s **1** (see schematic representation). Association constants are oligomer length specific, with a maximum value for the icosamer and docosamer. These oligomers have helical conformations that are highly shape-complementary to **1**; shorter and longer oligomers exhibit association constants roughly an order of magnitude smaller.

*Angew. Chem.* **2002**, *114*, 335–338



A. Tanatani, T. S. Hughes,  
J. S. Moore \* ..... 325–328

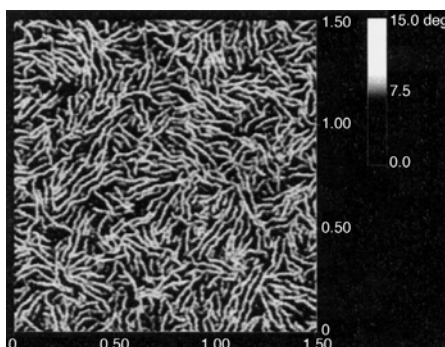
Foldamers as Dynamic Receptors: Probing the Mechanism of Molecular Association between Helical Oligomers and Rodlike Ligands

**Keywords:** chirality • foldamers • host–guest systems • molecular recognition • self-assembly



**Simply changing the solvent or evaporation conditions** enables the physical properties of polythiophene block copolymers and polyurethane elastomers to be controlled. The copolymers all have high conductivities as well as excellent film-forming and good mechanical properties, and well-defined nanowires that reach lengths in the micron range can be formed (see atomic force microscopy image).

*Angew. Chem.* **2002**, *114*, 339–342



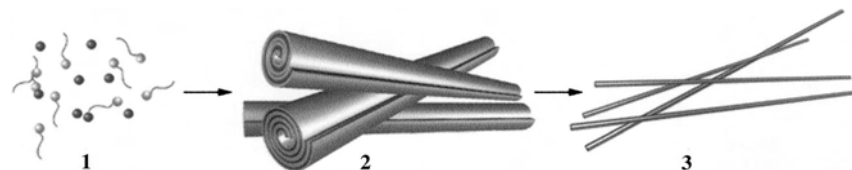
J. Liu, E. Sheina, T. Kowalewski,  
R. D. McCullough \* ..... 329–332

Tuning the Electrical Conductivity and Self-Assembly of Regioregular Polythiophene by Block Copolymerization: Nanowire Morphologies in New Di- and Triblock Copolymers

**Keywords:** conducting materials • nanostructures • polymers • self-assembly • thiophene



**Bulk quantities of uniform tungsten nanowires 3** with diameters of 20–80 nm and lengths ranging from 5 to 30 μm were obtained by a simple vacuum-controlled pyrolysis process from lamellar composites of WO<sub>4</sub><sup>2-</sup> ions and cetyltrimethylammonium (CTA<sup>+</sup>) surfactant ions. The lamellar composites were obtained from aggregates of CTA–WO<sub>4</sub> ion pairs (**1**). The cylindrical scrolls **2** are probably the first product of the pyrolysis; this confines the carbothermal reaction and results in the formation of the nanowires.



*Angew. Chem.* **2002**, *114*, 343–345

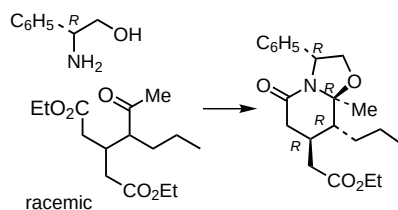
Y. D. Li,\* X. L. Li, Z.-X. Deng,  
B. C. Zhou, S. S. Fan, J. W. Wang,  
X. M. Sun ..... 333–335

From Surfactant–Inorganic Mesostructures to Tungsten Nanowires

**Keywords:** lamellar structures • nanostructures • surfactants • tungsten



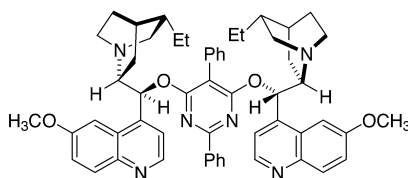
**Enantiotopic ester groups are desymmetrized** in the cyclodehydration of prochiral  $\delta$ -oxodiester with (*R*)-phenylglycinol. This reaction can be extended to racemic  $\delta$ -oxodiester, which undergo a tandem dynamic kinetic resolution–diastereoselective differentiation process (see scheme). The resulting bicyclic lactams can be used in the preparation of a variety of synthetically and pharmacologically interesting enantiopure piperidine derivatives.



*Angew. Chem.* **2002**, *114*, 345–348

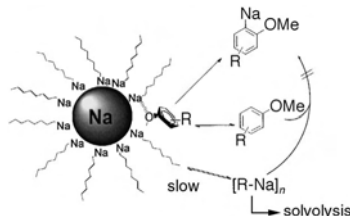


**The mechanism is not yet known** but the modified bisinchona alkaloid shown here is an excellent catalyst for the general and highly enantioselective 1,4-addition of thiols to cyclic enones. Selectivities ranging from 93 to >99% *ee* were achieved for the addition of 2-thionaphthol to six- to nine-membered enones.



*Angew. Chem.* **2002**, *114*, 348–350

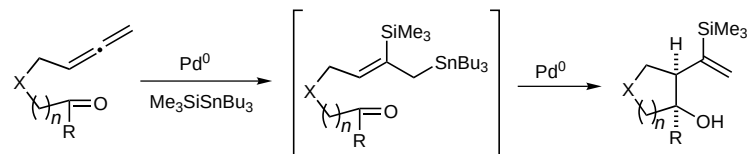
**Finely dispersed metallic sodium** in combination with an alkyl chloride RCl can replace organolithium reagents in the *ortho*-metalation of aromatic compounds (see scheme). The in situ generated base is consumed as soon as it is formed, which avoids Wurtz coupling, the usual side reaction, and the handling and storage of highly reactive alkyl sodium bases. Reaction conditions are mild, the reaction is easy to scale up, and the reagents needed are inexpensive.



*Angew. Chem.* **2002**, *114*, 350–353



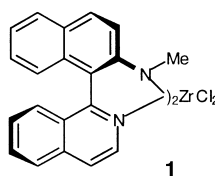
**Two in one:** the palladium-catalyzed regio- and diastereoselective silastannylation of allene aldehydes and ketones and the subsequent allyl addition to the carbonyl group gives rise to *cis*-cycloalkanols (see scheme; *n* = 1, 2; R = H, CH<sub>3</sub>; X = NTs, O, C(CO<sub>2</sub>Et)<sub>2</sub>, etc.). This tandem process requires a single catalyst and is carried out at a constant temperature.



*Angew. Chem.* **2002**, *114*, 353–355



**A long-lost cousin of the binaphthyl family has been found** to be readily accessible and configurationally stable. These so-called IAN-amines are competent ligands for Zr<sup>IV</sup> ions that display remarkable diastereoselectivity in the formation of C<sub>2</sub>-symmetric 2:1 complexes such as **1**. The ligands of the favored diastereomeric complex are homochiral despite the use of a racemic mixture to make the complex.



*Angew. Chem.* **2002**, *114*, 355–358

M. Amat,\* M. Cantó, N. Llor, V. Ponzo,  
M. Pérez, J. Bosch ..... 335–338

Dynamic Kinetic Resolution and Desymmetrization of Enantiotopic Groups by Cyclodehydration of Racemic or Prochiral  $\delta$ -Oxoesters with (*R*)-Phenylglycinol: Enantioselective Synthesis of Piperidines

**Keywords:** diastereoselectivity • dynamic kinetic resolution • lactams • nitrogen heterocycles • synthetic methods

P. McDavid, Y. Chen, L. Deng\* ..... 338–340

A Highly Enantioselective and General Conjugate Addition of Thiols to Cyclic Enones with an Organic Catalyst

**Keywords:** asymmetric catalysis • cinchona alkaloids • enones • Michael addition • thiols

A. Gissot, J.-M. Becht, J. R. Desmurs,  
V. Pèrière, A. Wagner,\* ..... 340–343

Directed *ortho*-Metalation, a New Insight into Organosodium Chemistry

**Keywords:** metalation • sodium • substituent effects • synthetic methods

S.-K. Kang,\* Y.-H. Ha, B.-S. Ko, Y. Lim,  
J. Jung ..... 343–345

Palladium-Catalyzed Regio- and Diastereoselective Tandem Silastannylation/Allyl Addition of Allene Aldehydes and Allene Ketones: Synthesis of *cis* Cyclopentanol and Cyclohexanol

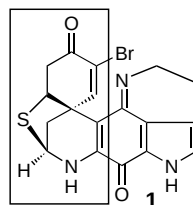
**Keywords:** allenes • allylic compounds • cyclization • homogeneous catalysis • silastannylation

S. B. Cortright, J. N. Johnston\* ..... 345–348

IAN-Amines: Direct Entry to a Chiral C<sub>2</sub>-Symmetric Zirconium(IV)  $\beta$ -Diketamine Complex

**Keywords:** biaryls • N ligands • zirconium

**A concise and efficient method to construct** the characteristic sulfur-cross-linked core of an unprecedented antitumor marine alkaloid, discorhabdins, has been developed. By utilizing this methodology the first total synthesis of (±)-discorhabdin A (**1**) has been achieved.



H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, M. Egi, Y. Kita\* . . . . 348–350

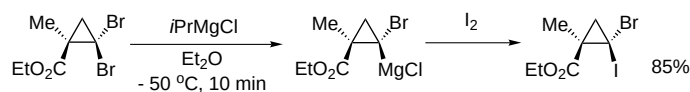
Synthetic Studies on the Sulfur-Cross-Linked Core of Antitumor Marine Alkaloid, Discorhabdins: Total Synthesis of Discorhabdin A

**Keywords:** alkaloids • nitrogen heterocycles • spiro compounds • sulfur heterocycles • total synthesis

*Angew. Chem.* **2002**, *114*, 358–360



**An I–Mg or Br–Mg exchange reaction** has enabled ester-functionalized cyclopropylmagnesium derivatives including magnesium carbenoids to be prepared for the first time in high yield. These magnesium reagents are configurationally stable and react stereoselectively with electrophiles (see scheme).



*Angew. Chem.* **2002**, *114*, 361–362

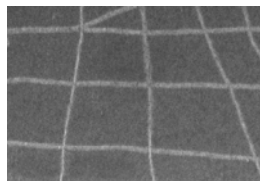
V. A. Vu, I. Marek, K. Polborn, P. Knochel\* . . . . . 351–352

Preparation of New Functionalized Cyclopropylmagnesium Reagents

**Keywords:** carbenoids • halogen–metal exchange • magnesium • small ring systems • stereoselectivity



**A “minimal-lithography” technique** for chemically assembling small deterministic crossbars of single-walled carbon nanotube (SWNT) ropes: The formation of electrically conducting crossbar circuits with 8 to 14 junctions (see picture) from a suspension of SWNTs is described. The critical structural parameters of the circuits were controlled by chemically directed self-assembly, rather than lithographic patterning, and all steps were carried out under ambient conditions.



M. R. Diehl, S. N. Yaliraki, R. A. Beckman, M. Barahona, J. R. Heath\* . . . . . 353–356

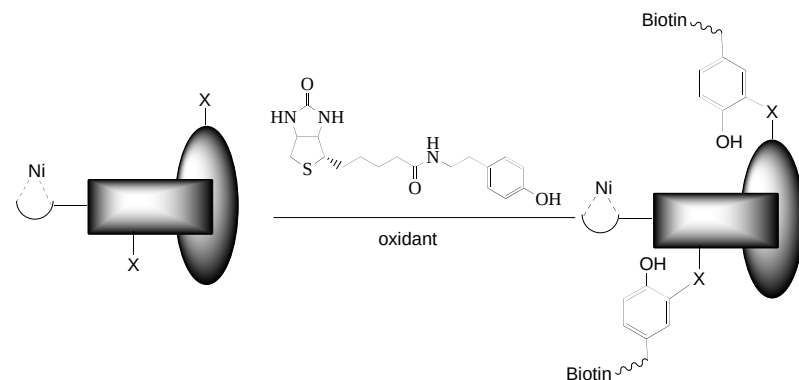
Self-Assembled, Deterministic Carbon Nanotube Wiring Networks

**Keywords:** conducting materials • nanostructures • nanotubes • self-assembly

*Angew. Chem.* **2002**, *114*, 363–366



**A useful method for identifying the binding partners** of a given protein: The complex of Ni<sup>II</sup> with the tripeptide NH<sub>2</sub>-glycine-glycine-histidine or the hexahistidine peptide mediates biotinylation of proximal proteins through an oxidatively triggered reaction (see scheme).



F. Amini, T. Kodadek,\* K. C. Brown\* . . . . . 356–359

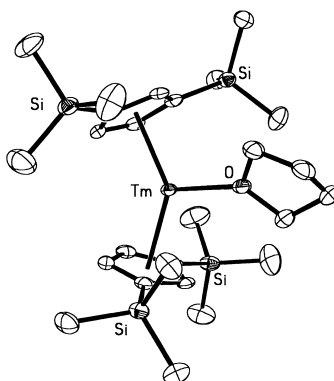
Protein Affinity Labeling Mediated by Genetically Encoded Peptide Tags

**Keywords:** affinity labeling • biotinylation • nickel • oxidation • proteins

*Angew. Chem.* **2002**, *114*, 366–369

**The right choice** of solvents, ligand ( $[\text{C}_5\text{H}_3(\text{SiMe}_3)_2]^-$ ), and reaction conditions has facilitated the isolation and structural characterization of the first  $\text{Tm}^{\text{II}}$  metallocene (see picture). In situ organometallic chemistry of the even more reducing  $\text{Dy}^{\text{II}}$  ion, namely a dinitrogen reduction to give the  $\text{Dy}^{\text{III}}$  dinitrogen complex  $[[[\text{C}_5\text{H}_3(\text{SiMe}_3)_2]_2\text{Dy}]_2\text{N}_2]$ , reveals the importance of carrying out such reactions in an atmosphere more inert than nitrogen.

*Angew. Chem.* **2002**, *114*, 369–371



W. J. Evans,\* N. T. Allen,  
J. W. Ziller ..... 359–361

Expanding Divalent Organolanthanide Chemistry: The First Organothulium(II) Complex and the In Situ Organodysprosium(II) Reduction of Dinitrogen

**Keywords:** cyclopentadienyl ligands • dysprosium • lanthanides • metallocenes • thulium



Supporting information on the WWW  
(see article for access details).

\* Author to whom correspondence should be addressed



Accelerated publications

The electron microscopy pictures were taken by Dr. Perer Herter, and the cover picture was designed and prepared by Gesine Schulte (both at the MPI für Molekulare Physiologie Dortmund).



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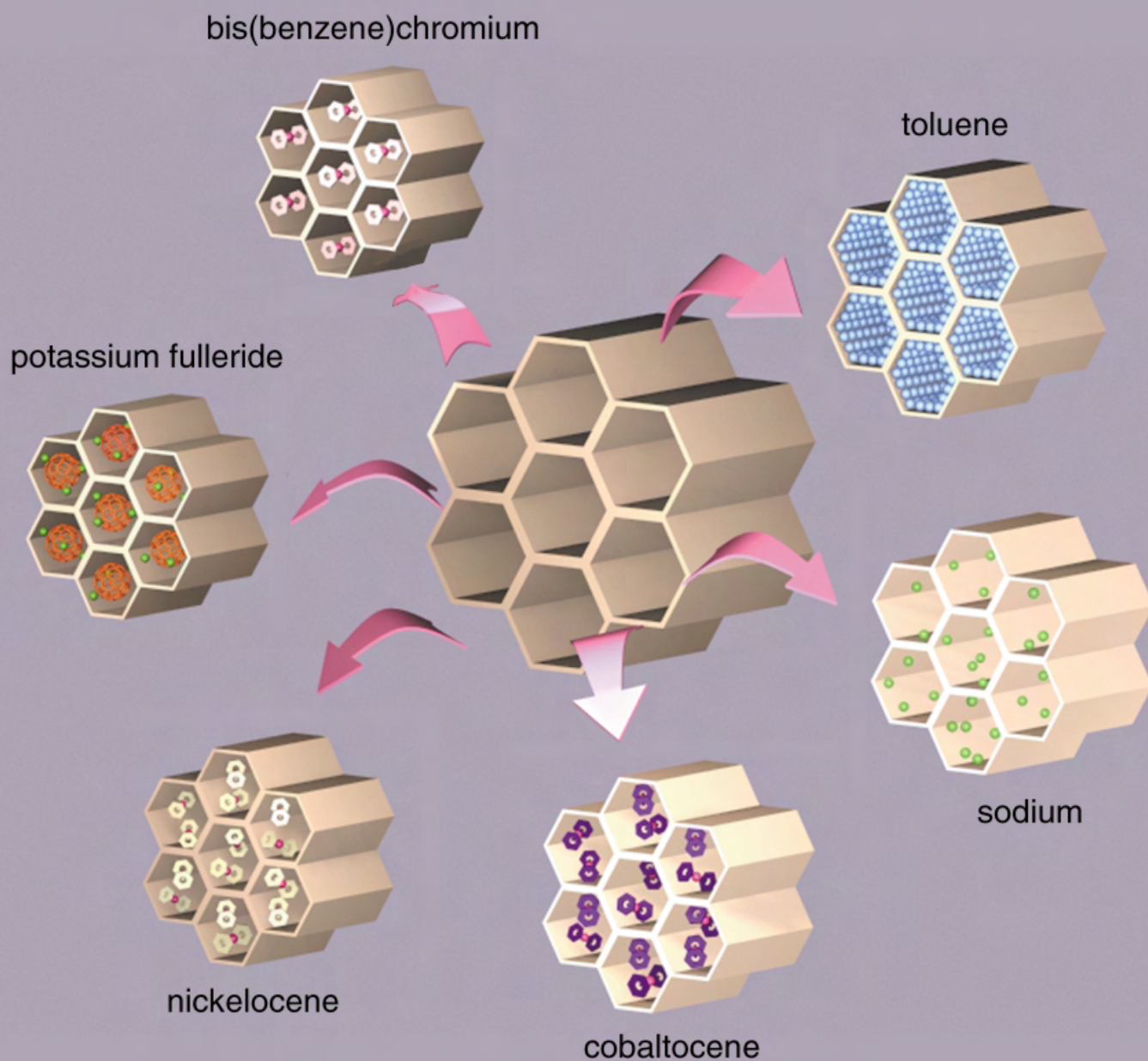
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**I**ntercalation into mesoporous materials that contain transition metals (e.g., niobium oxide) allows the production of a variety of structures with unique properties.



# Recent Advances in Synthesis and Applications of Transition Metal Containing Mesoporous Molecular Sieves

Xun He and David Antonelli\*

Work in mesoporous silica-based materials began in the early 1990s with work by Mobil. These materials had pore sizes from 20–500 Å and surface areas of up to 1500 m<sup>2</sup> g<sup>-1</sup> and were synthesized by a novel liquid crystal templating approach. Researchers subsequently extended this strategy to the synthesis of mesoporous transition metal oxides, a class of materials useful in catalysis, electronic, and magnetic applications because of variable oxidation states, and populated d-bands—

features not found in silicates. These materials are already showing promise in electronic and optical applications hinging on the semiconducting properties of transition metal oxides and their potential to act as electron acceptors, an important feature in the design of cathodic materials. This is the first general review of non-silicate mesoporous materials and will focus on recent advances in this area, emphasizing materials possessing unique electronic, magnetic, or optical properties. Also

covered are advances in the synthesis and applications of mesostructured sulfides as well as a new class of template-synthesized platinum-based materials that show promise in heterogeneous catalysis.

**Keywords:** electronic properties • mesoporous materials • semiconductors • solid-state structures • template synthesis

## 1. Introduction

In the wake of a great expansion of interest in the design and synthesis of materials with tailored chemical and physical properties, materials scientists have focused much attention on shape-controlled composite materials, with the goal being to create systems in which there is functional cooperation between the overall nanoscale architecture of the material and its physical properties. Multilayered nanotubes,<sup>[1]</sup> imprinted polymers,<sup>[2]</sup> polymer-encapsulated drug delivery systems,<sup>[3]</sup> and “artificial leaf” technologies<sup>[4]</sup> are examples of systems that weave two or more disparate materials into a single whole, which possesses electronic, mechanical, or optical properties not possible in more simple single-phase bulk systems. A crucial feature in the design of many functional materials is controlled porosity over a broad length scale. Advances by Mobil researchers in the 1990s led to the discovery of MS41 mesoporous silicates, a family of materials with regularly spaced nanometer-sized pores, synthesized by using liquid crystals as structural imprints to cast the shape of the silica.<sup>[5–12]</sup> Since this work, researchers have expanded this

basic motif to the point where it is possible to synthesize fabricated architectures with a myriad of structural features and pore sizes ranging from 1–10000 nm out of virtually any stable solid substance that can be easily manipulated on the nanoscale.<sup>[13]</sup> Single molecules,<sup>[14]</sup> self-assembled surfactant phases,<sup>[15]</sup> amphiphilic block copolymers,<sup>[16, 17]</sup> vesicles,<sup>[18]</sup> emulsion-stabilized oil droplets,<sup>[19]</sup> and even micron-level latex spheres<sup>[20, 21]</sup> have all been used in this regard, the last example being of particular importance to the fabrication of photonic band-gap materials.<sup>[22]</sup> Transition metals and transition metal oxides are of particular interest in the synthesis of ordered materials because of their variable oxidation states, properties not possessed by silicates, a capacity which often leads to unusual magnetic, electronic, and optical properties.

After pioneering efforts leading to the synthesis of mesostructured W and Pb oxides in 1993,<sup>[23]</sup> a stable mesoporous Nb oxide molecular sieve was reported in 1996.<sup>[24, 25]</sup> This material had an advantage over the W and Pb materials in that the pore structure remained intact after template removal. Shortly thereafter the synthesis of related mesoporous Zr, Ti, Ta, Hf, and Mn oxides,<sup>[26–38]</sup> were reported, the last example being of special note since it was the first such material with semiconducting properties,<sup>[38]</sup> an important feature in many catalytic and electronic applications. More recently, Ozin and co-workers reported the synthesis of mesoporous yttrium-doped zirconium oxide materials with high ion conductivity for fuel-cell applications.<sup>[39]</sup> Kanatzidis and co-workers<sup>[40]</sup> and

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E-mail: danton@server.uwindsor.ca

Ozin and co-workers<sup>[41]</sup> independently synthesized mesoporous Ge sulfide based materials with semiconducting properties. Research in our group has focused on the reduction and modification of existing mesoporous Nb, Ti, and Ta oxides,<sup>[42, 43]</sup> to lead to numerous organometallic/inorganic composites with semiconducting, metallic, superparamagnetic, and even spin-glass behavior. This review will focus principally on these and other recent advances in electroactive molecular sieves, an exciting and rapidly growing area of research interest.

## 2. Electroactive Mesoporous Transition Metal Oxides

### 2.1. Mesoporous Zirconium Oxide Based Systems for Fuel-Cell Applications

Solid oxide fuel cells (SOFC) have attracted much recent attention in the fields of materials science, catalysis, ceramics, and electrochemistry.<sup>[44]</sup> Much of this research is aimed at the design of electrode materials which are not only stable under high operating temperatures (600–1000 °C), but also have optimal electronic and ionic conductivity coupled with catalytic activity and mass-transfer properties. The traditional electrode materials are nickel/yttrium oxide-stabilized-zirconium oxide (Ni-YSZ) cermet (ceramic/metal) as the anode and perovskite or platinum/yttrium oxide-stabilized-zirconium oxide (Pt-YSZ) as the cathode. The common approach to improve the performance of the materials is to enlarge the triple-phase boundary (TPB), which controls the efficiency of the SOFCs, by decreasing the dimensions of the active metal

particles, Ni or Pt, relative to that of the yttrium oxide-stabilized-zirconium oxide grains. Several researchers have attempted to improve the porosity and enlarge the TPB of the materials by manipulating the microstructure of electrode materials through traditional nanofabrication techniques,<sup>[45]</sup> but most of these materials are just nanoscale or microscale versions of the bulk cermet electrode ceramics with a comparatively low thermal stability and wide pore-size distribution.

Ozin's group recently reported the first example of binary and ternary mesoporous yttrium oxide-stabilized-zirconium oxide (meso-YSZ) and metal (Pt, Ni)- yttrium oxide-zirconium oxide solid solutions which could be used as solid oxide fuel-cell electrode materials.<sup>[39, 46, 47]</sup> While much work has gone into the synthesis of stable mesoporous zirconium oxides, including an elegant recent example from Rao's group<sup>[48]</sup> demonstrating an unusual lamellar-to-hexagonal-to-cubic phase change (Figure 1), these materials differ from previous efforts in that they use yttrium as a stabilizing agent. These mesoporous yttrium oxide-stabilized-zirconium oxide materials were synthesized by modified sol-gel methods under basic conditions, where zirconium ethoxide and yttrium acetate were used as the precursors for the transition metal oxides, and the cationic surfactant, cetyltrimethylammonium bromide (CTAB) was used as the mesostructure-directing reagent. The higher dielectric constant and coordinating ability of ethylene glycol was able to control the rate of hydrolysis and avoid the solubility problems which previously resulted in low levels of yttrium oxide incorporation in the zirconium oxide phase.<sup>[49]</sup> The surfactant template was removed by calcining the as-synthesized materials at various

*David Antonelli was born in Chicago in 1963 and raised in The United States, Great Britain, and Canada. He completed his BSc at the University of Alberta in 1987 and his PhD in organometallic chemistry with Martin Cowie at the University of Alberta three years later at the end of 1990. He was an NSERC postdoctoral fellow in organometallic chemistry at Oxford University with M. L. H. Green in 1991, and at Caltech in 1992–93 with John E. Bercaw. After completing a postdoctoral term in Ziegler-Natta catalysis with Jeffrey Stryker at the University of Alberta in 1993, he moved on to study nanoporous materials as a postdoctoral associate with Prof. J. Y. Ying at the Massachusetts Institute of Technology Department of Chemical Engineering from 1994–1996. In 1997 he took up a lectureship at The University of Sussex School of Chemistry, Physics, and Environmental Science before returning to Canada in 1998 as an Associate Professor in Chemistry at the University of Windsor. He currently directs a research group focused on the electronic and catalytic properties of nanoporous materials with variable oxidation states and conducting molecular wires in the pores. He is the author of over 40 publications and was the winner of the Ontario Premier's Research Excellence Award, The University of Windsor Excellence in Research and Scholarship Award, and a Royal Society of Britain Research Award.*



D. Antonelli



X. He

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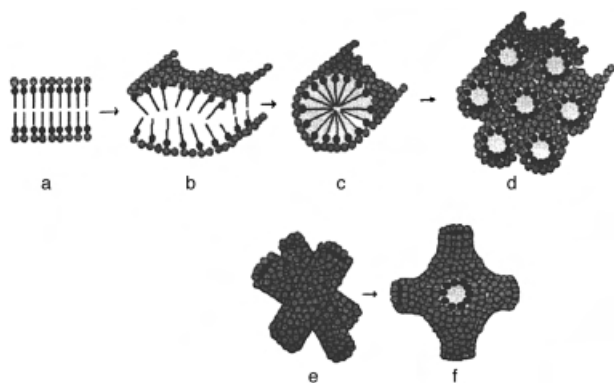


Figure 1. Schematic representation of lamellar-to-hexagonal phase transformation (a–d) and the hexagonal-to-cubic transformation (e and f) in mesostructured zirconium oxide. Reproduced with permission from ref. [48].

rates and temperatures. The yttrium content in these binary materials can be tuned from 12–56 wt% and no phase segregation of yttrium oxide and zirconium oxide was observed. The nitrogen adsorption isotherms of these materials after calcination gave Brunauer–Emmett–Teller (BET) surface areas ranging from 100–300 m<sup>2</sup> g<sup>−1</sup>, and an average pore size of 18–21 Å. The pore wall was determined to be 25–28 Å thick and composed of nanocrystalline yttrium oxide-stabilized zirconium oxide. The synthetic strategy is outlined in Figure 2. The variable-temperature powder X-ray diffraction patterns illustrated the high structural stability of these materials at temperatures above 600 °C, a property crucial for useful solid oxide fuel-cell materials. This material possesses the highest surface area of any recorded sample of template-free yttrium oxide stabilized zirconium oxide.

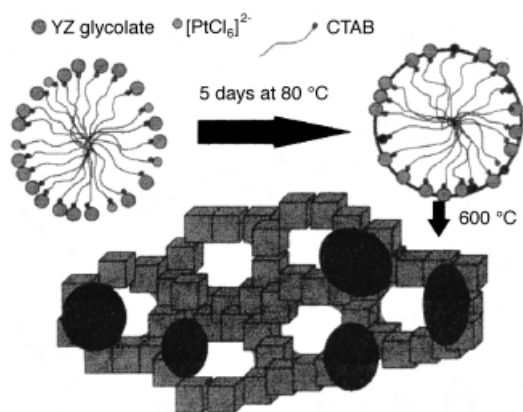


Figure 2. Self-Assembly of anionic yttrium–zirconium glycolate and hexachloroplatinate precursors with a supramolecular cationic surfactant template leading to the formation of a mesoporous material denoted *meso*-PtYZ. Reproduced with permission from ref. [46].

Electroactive ternary mesoporous metal (Pt, Ni) yttrium oxide zirconium oxide, were synthesized by using metal precursors, such as sodium hexachloroplatinate, or Ni<sup>II</sup> reagents, that is, bis(acetato) nickel, nickel chloride, or nickel nitrate as the source of the third metal dopant in the presence of surfactant-containing yttrium oxide zirconium oxide gels.<sup>[46, 47]</sup> This method produced ternary transition metal oxides with pore structures similar to those of the meso-

YSZ materials. The inclusion of Ni or Pt in the materials is necessary for applications in fuel cells, as it effects the charge-transfer and oxygen-transport properties. In these materials platinum and nickel exist as metal (Pt) and metal oxide (NiO<sub>1+x</sub>) nanoclusters, respectively, 30–40 Å in size, homogeneously dispersed throughout the yttrium oxide zirconium oxide mesostructures. The amount of Pt and Ni can be tuned from 1–10 wt % and 10–30 wt %, respectively. A chemisorption titration experiment on meso-Pt-YSZ by use of H<sub>2</sub>–O<sub>2</sub> adsorbents showed that the surface area of the incorporated platinum nanoclusters was partly accessible to gaseous reagents and gave a representative dispersion of 18% for a sample loading of 2.4 wt % Pt. The ionic conductivity of meso-Pt (NiO)-YSZ materials was evaluated by alternating current (AC) complex impedance spectroscopy in the temperature range of 300–800 °C and recorded in an air atmosphere. The meso-YSZ and meso-Pt-YSZ samples gave a single symmetric, slightly depressed semicircle from 500–700 °C, which results from both bulk and grain boundary polarization and all the meso-NiO-YSZ samples yielded similar impedance spectra. The bulk and grain boundary conductivity of all meso-Pt(NiO)-YSZ samples was extracted from the low-frequency minima of the respective semicircles in the Argand plots of the complex impedance spectra (Figure 3). The corresponding activation energies  $E_a$  for thermally activated charge-transported process were obtained from the Arrhenius equation  $\sigma = (A/T)\exp(E_a/RT)$ . These data are summarized in Table 1.

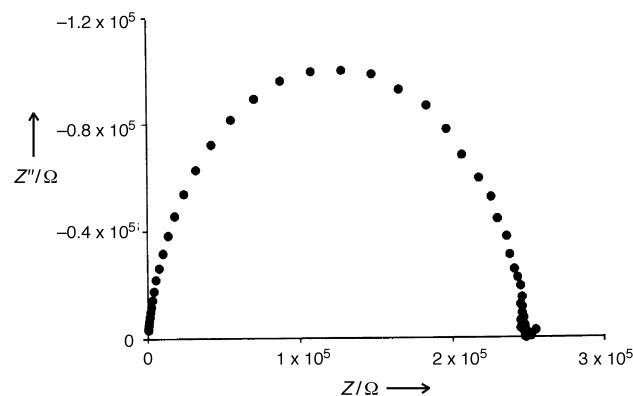


Figure 3. Complex impedance Argand plot for meso-NiO-YSZ with 22 wt % NiO recorded at 296 °C in air.<sup>[47]</sup>

Table 1. Conductivities ( $\sigma$ ) [ $\Omega^{-1}\text{cm}^{-1}$ ] and corresponding activation energies [kJ mol<sup>−1</sup>] of mesoporous Pt(NiO)-YSZ samples.

|                             | Pt-YSZ | Pt-YSZ               | Pt-YSZ               | Ni-YSZ               | Ni-YSZ               | Ni-YSZ               |
|-----------------------------|--------|----------------------|----------------------|----------------------|----------------------|----------------------|
| wt % (Pt or NiO)            | 2      | 17                   | 23                   | 7                    | 22                   | 27                   |
| $E_a$                       | 207    | 130                  | 93                   | 67                   | 53                   | 36                   |
| $\sigma(450^\circ\text{C})$ | –      | $3.4 \times 10^{-8}$ | $5.5 \times 10^{-5}$ | $1.2 \times 10^{-7}$ | $6.2 \times 10^{-6}$ | $2.9 \times 10^{-5}$ |

The mixed oxygen-ion electron charge transport was dominated by the nonstoichiometric nickel oxide nanocrystalline phase at low temperature (around 400 °C) in the meso-NiO-YSZ. The enhanced NiO connectivity within meso-NiO-YSZ forms an electronic conduction pathway at far lower NiO content than in conventional materials (little change  $E_a = 80$ –

100 kJ mol<sup>-1</sup> with NiO content from 0–40 mol %). However, the slightly higher activation energies for oxygen ion charge transport in the meso-Pt-YSZ materials as compared to conventional Pt-YSZ were also observed maybe as a result of the nanocrystalline YSZ channel walls. These two materials represent a new class of solid fuel-cell electrode materials and show some of the first potential applications of mesoporous transition metal oxides.

## 2.2. Semiconducting Mesoporous Manganese Oxides

Transition metal oxides have variable oxidation states and *d* electrons, these properties offers advantages over aluminosilicate materials, thus the direct chemical syntheses of mesoporous transition metal oxides with partially filled *d* shells should lead to materials with unusual electronic, magnetic, and catalytic properties. However, most of the mesoporous transition metal oxides synthesized to date, including Ti,<sup>[32]</sup> Nb,<sup>[24, 25]</sup> Ta,<sup>[28]</sup> W,<sup>[23]</sup> Zn,<sup>[50]</sup> V,<sup>[51]</sup> Zr,<sup>[29–31]</sup> and Hf<sup>[33]</sup> are insulators containing high-valent transition metals in a single oxidation state. Recently Suib's group reported hexagonal and cubic phases of mesoporous manganese oxides with mixed oxidation states. These phases were synthesized using surfactants as mesostructure directing agents. These materials represented the first semiconducting mesostructures and possess catalytic activity in the oxidation of alkanes.<sup>[38]</sup> The mixed oxidation states (III/IV) of manganese in these materials result from the oxidation of the metal precursor Mn(OH)<sub>2</sub> (or Mn(OH)<sub>6</sub><sup>4+</sup>) by air during the synthetic process. The calcined samples prepared with higher surfactant concentration (28 wt %) had hexagonally ordered manganese oxide channels (MOMS-1), while lower concentration (10 wt %) of surfactant resulted in cubic mesostructures (MOMS-2). The argon adsorption isotherms of MOMS-1 and MOMS-2 gave BET surface areas of 170 m<sup>2</sup> g<sup>-1</sup> and 46 m<sup>2</sup> g<sup>-1</sup>, respectively, while the pore sizes and wall thicknesses were 30 and 17 Å, respectively. The walls of the mesopores are composed of microcrystallites of dense phase of Mn<sub>2</sub>O<sub>3</sub> and Mn<sub>3</sub>O<sub>4</sub> (average oxidation states of Mn in MOMS-1 is 3.55) with MnO<sub>6</sub> octahedra as the primary building blocks which are linked together by sharing edges. This is an important advance because most mesoporous materials possess amorphous walls, an undesirable feature in many catalyst supports. No other phases or amorphous manganese oxides were observed by transmission electron microscopy (TEM) or X-ray diffraction (XRD) methods. The conductivities of MOMS-1 before and after calcination are 5.0 × 10<sup>-8</sup> and 8.1 × 10<sup>-6</sup> Ω<sup>-1</sup> cm<sup>-1</sup>, respectively (the band gap from UV spectra for the calcined material is 2.46 eV), while the conductivity of MOMS-2 is 2.28 × 10<sup>-6</sup> Ω<sup>-1</sup> cm<sup>-1</sup>. These materials were the first semiconducting mesostructures and for this reason may have applications in photocatalysis or the fabrication of novel optic and electronic devices. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) demonstrated that both MOMS materials are stable at up to 1000 °C. The Fourier transform infrared (FT-IR) data for pyridine adsorbed on calcined MOMS-1 indicate that there

are two types of Lewis acid sites. This result is further supported by the observation that MOMS-1 can act as an active oxidation catalyst in the oxidation of cyclohexane and *n*-hexane to the corresponding alcohols in aqueous solutions.

## 2.3. Hierarchically Templated Mixed-Valent Molybdenum Oxides

In 1999 our group reported a semiconducting mesostructured mixed oxidation state molybdenum oxide, a material which selectively forms toroidal shapes with diameter of several hundred nanometers.<sup>[52]</sup> This material was prepared by use of an as-synthesized dimeric molybdenum ethoxide complex with a bridging dodecylimido group as structure-constructing blocks and then hydrolyzing to generate a bronze mesostructure Mo oxide. The XRD pattern showed a high intensity peak (100) at *d* = 32 Å. The X-ray photoelectron spectrum (XPS) displayed Mo 3d<sub>5/2</sub> emissions which could be simulated as three peaks at 231.9, 232.8, and 230.9 eV. The peak at 232.8 eV can be assigned to Mo<sup>V</sup>, and the gap from valance band to Fermi level is 1.3 eV (band gap calculated from UV is 3.75 eV), which provides evidence for weakly semiconducting properties in this material.

The toroidal structures of this material, which are constructed of oriented mesotubules of roughly 50 nm in length and 3 nm in diameter, were revealed by transmission electron microscopy (TEM) images (Figure 4a). The toroidal shapes were thought to arise from a double templating interaction where the amine template forms both micelles and vesicles or microbubbles under the same conditions.<sup>[53, 54]</sup> Attempts to remove the template either by acid treatment or ozone treatment led to the formation of layered and amorphous materials, respectively. Figure 4b shows TEM images which provide evidence for an unusual dynamic process in which adjacent toroids open up and coalesce into much larger toroids. This was the first example of dynamic behavior in such hierarchically ordered materials and is a similar process to that observed in bundles of carbon nanotubes at high temperature.<sup>[55]</sup>

When these bronze toroidal mesoporous materials were hydrothermally treated in a sealed tube at 150 °C for ten days, a phase changed to a new blue material consisting of 2–3 nm Mo<sup>IV</sup> oxide crystallites (Figure 4c), thought to arise from crystallization of the walls, and a mesolamellar Mo<sup>VI</sup> region (Figure 4d) as indicated by XRD and TEM. The conductivity of this blue material is 6.3 × 10<sup>-7</sup> Ω<sup>-1</sup> cm<sup>-1</sup>, higher than that of the bronze compound, possibly because of the presence of metallic Mo<sup>IV</sup> oxide. The XPS supports the presence of a metallic phase with a weak emission near the Fermi level. While MOMS mesoporous manganese oxide materials possess crystalline walls, in the case of these molybdenum oxide toroids, crystallization of the walls leads to collapse of both the mesostructure and the macrostructure, which suggests that long-range order in the walls in many cases may come at the expense of the porous structure.



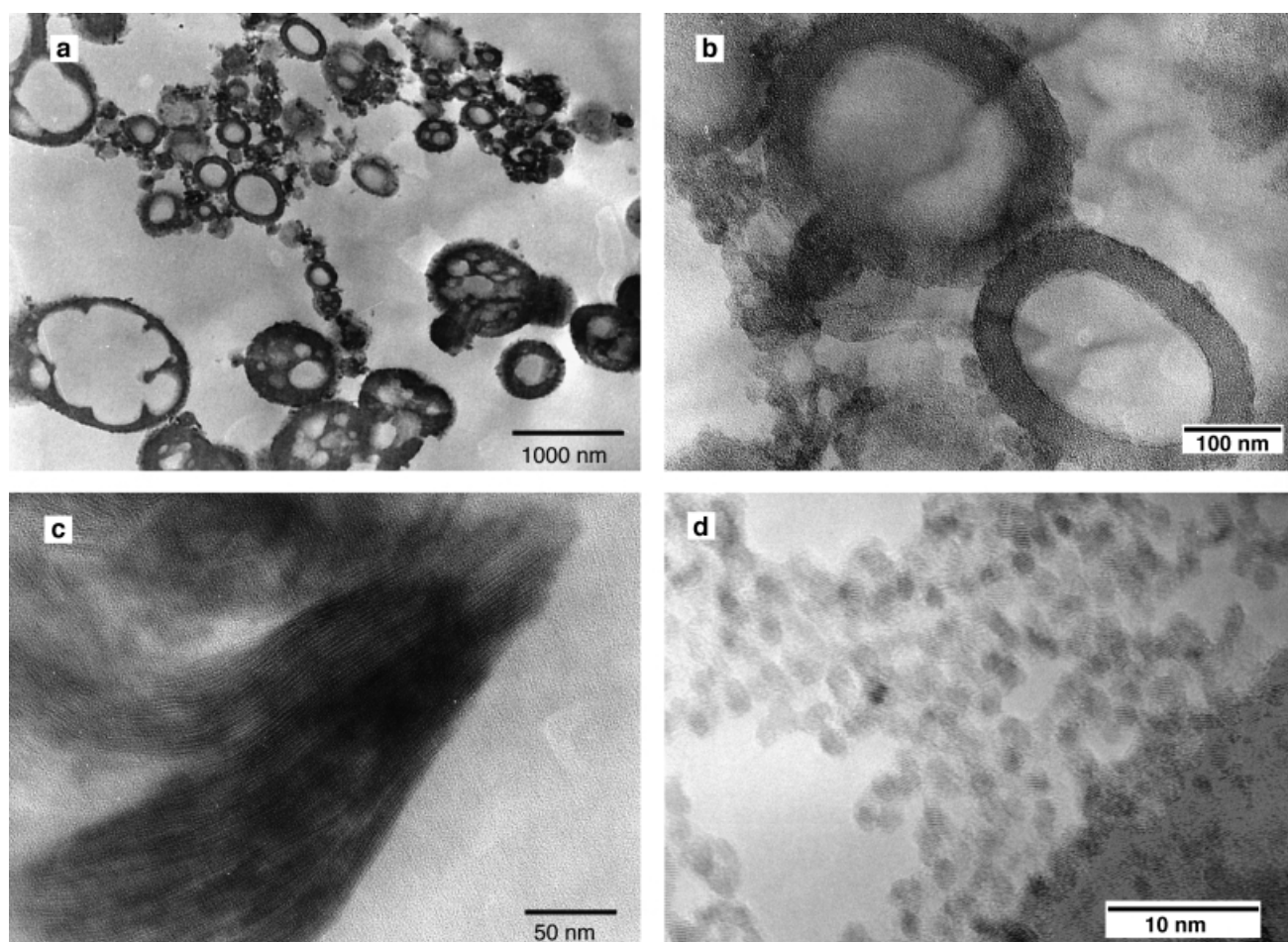


Figure 4. TEM images of molybdenum oxide bronzes a) at low magnification revealing the toroidal structures of approximately 300 nm in diameter including regions in which several smaller toroids have clustered together inside a larger toroid. These living-cell-like regions reorder into larger toroids upon exposure to the TEM electron beam, b) higher magnification reveals the mesostructured nature of the walls of the toroid. Scanning electron microscopy (SEM) revealed no salient structural features or tubular forms, which indicates that these toroids are relatively flat (ca. 50 nm). Other areas of sample exist in which there is no higher order to the mesostructured system, although the toroidal regions dominate the material, c) lamellar region of the mesostructured molybdenum oxide blue showing that certain regions of the bronze have reordered into a layered phase in the blue, d) close up of a region of the molybdenum blue showing where crystallization of the walls of the mesostructure into oxide grains approximately 1.5 nm in size has led to partial degradation of the occluded mesopores. Samples were prepared either by sonication in isopropanol or microtoming followed by deposition on a carbon-coated copper grid. Micrographs were recorded at 300 KV on a Hitachi H-9000 STE microscope.<sup>[52]</sup>

#### 2.4. Photocatalytic Activity of Mesoporous Niobium and Phosphated Titanium Oxides

An important area of application of mesoporous transition metal oxides is in photocatalysis. In the past decade, a variety of photocatalytic systems centered around oxidative degradation of organic chemicals,<sup>[56, 57]</sup> fixation of carbon dioxide,<sup>[58–60]</sup> evolution of H<sub>2</sub> from water,<sup>[61, 62]</sup> and the reduction of metal ions<sup>[63]</sup> were developed using semiconducting transition metal oxides. Coupling the controlled pore size and high surface areas of mesoporous materials with photocatalytic properties would thus represent an important advance. Titanium dioxide, because of its efficient electron-hole pair separation and low cost, is one of the most desirable materials for photocatalytic applications. In 1998 Stone and Davis studied the photocatalytic activity of phosphated titanium and niobium oxide based mesoporous molecular sieves.<sup>[64]</sup> The well-known oxidative dehydrogenation of 2-propanol to acetone was used as a probe to measure the photocatalytic activity of the materials. The quantum yields were defined as

the molecules of acetone formed per incident photon (wavelength of light as incident light resource was about 360 nm). The surface areas, band gaps, and quantum yields of the phosphated titanium and niobium oxide catalysts are summarized in Table 2.

Table 2. Characterization and reactivity results for titanium and niobium materials.

| Samples                                          | Surface area<br>[m <sup>2</sup> g <sup>-1</sup> ] | Band gap<br>[eV] | Quantum yield<br>$\phi$ |
|--------------------------------------------------|---------------------------------------------------|------------------|-------------------------|
| meso-TiO <sub>2</sub> (473 K) <sup>[a]</sup>     | 712                                               | 3.19             | 0.0026                  |
| meso-TiO <sub>2</sub> (973 K) <sup>[a]</sup>     | 90                                                | 3.25             | 0.0089                  |
| meso-TiO <sub>2</sub> , extracted                | 603                                               | 3.15             | 0.010                   |
| ns-TiO <sub>2</sub> , as-synthesized             | –                                                 | 3.24             | 0.0094                  |
| ns-TiO <sub>2</sub> (873 K), <sup>[a]</sup> 1 h  | 39                                                | –                | 0.022                   |
| ns-TiO <sub>2</sub> (873 K), <sup>[a]</sup> 3 h  | 36                                                | 3.22             | 0.038                   |
| ns-TiO <sub>2</sub> (873 K), <sup>[a]</sup> 12 h | 28                                                | 3.26             | 0.27                    |
| Anatase (Aldrich)                                | 9                                                 | 3.28             | 0.41                    |
| Degussa P25                                      | 50                                                | 3.22             | 0.45                    |
| meso-Nb <sub>2</sub> O <sub>5</sub>              | 415                                               | 3.29             | 0.0041                  |
| Nb <sub>2</sub> O <sub>5</sub>                   | 13                                                | 3.08             | 0.217                   |

[a] The calcining temperature is given in parenthesis.

The lower photocatalytic activity of mesoporous titanium and niobium oxides compared to the anatase phase was attributed to the amorphous nature of the walls of these materials and the presence of phosphorous in the case of the titanium dioxide materials: the low degree of crystalline wall and the high surface concentration of defects lead to surface electron-hole recombination, and/or the poisoning of catalytic surface sites by the phosphorous remaining from the templates. Since high surface area mesoporous titanium dioxide is now readily available, the presence of phosphorous in these materials should no longer hinder applications,<sup>[36]</sup> although from these studies it appears that the low crystallinity of the walls of the structure may be a larger hurdle to overcome before the development of functional mesoporous titanium oxide photocatalysts can be realized.

## 2.5. Photocatalytic Activity of Mesoporous Tantalum Oxides

Takahara and Domen et al. recently reported the photocatalytic activity of mesoporous tantalum oxide.<sup>[65]</sup> These studies were undertaken because Ta-based mixed oxides are highly active in the overall decomposition of water under UV irradiation.<sup>[66–68]</sup> When as-synthesized tantalum oxide, prepared by the method of Antonelli and Ying, was used as a photocatalyst, H<sub>2</sub> evolved in a speed of 50  $\mu\text{mol h}^{-1}$ . In contrast, the sample calcined at 600 K, after template removal by acid treatment and solvent extraction, showed higher photocatalytic activity and released both H<sub>2</sub> and O<sub>2</sub> in a stoichiometric ratio, even though a brief induction period was observed. The initial H<sub>2</sub> evolution was attributed to the decomposition reaction of the remaining surfactants and the stoichiometric evolution of H<sub>2</sub> and O<sub>2</sub> started after complete consumption of the surfactant template. A NiO loaded sample showed higher photocatalytic activity and shorter induction time than those samples without NiO because NiO can act as cocatalyst in the water decomposition reaction (Figure 5). The optimal NiO loading level for the overall water decomposition was found to be 4.0 wt %. The NiO loaded samples showed an important trend in increasing photocatalytic activity. These results are summarized in Table 3.

Mesoporous Ta<sub>2</sub>O<sub>5</sub> samples showed better photocatalytic activity than the non-porous amorphous and crystallized samples because of its higher surface area which results in a higher NiO loading level. These high activities as compared to those reported above for titanium and niobium oxides<sup>[64]</sup> were

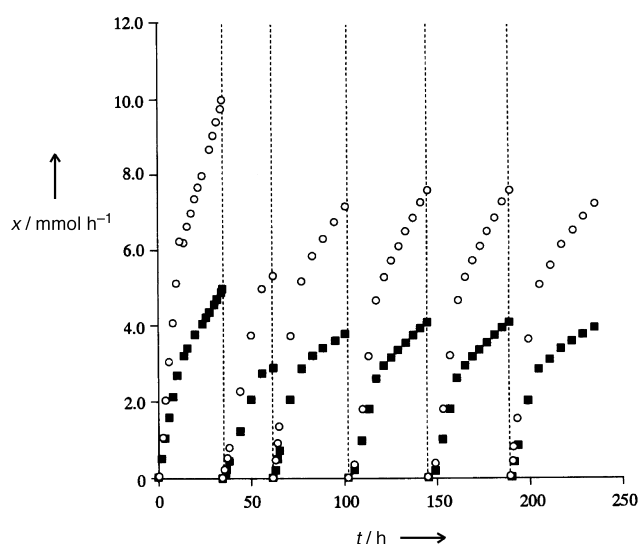


Figure 5. Time course of photocatalytic decomposition of water over NiO (4 wt %)-loaded mesoporous Ta<sub>2</sub>O<sub>5</sub> after R673-0473 treatment: reduction at 673 K by H<sub>2</sub> followed by reoxidation in O<sub>2</sub> at 473 K. Reproduced with permission from ref. [65].

explained by the different band gaps of the respective materials. The stable photocatalytic activity of pretreated mesoporous Ta<sub>2</sub>O<sub>5</sub> with 4 wt % NiO continued for more than 200 hours although the first run exhibited somewhat higher activity. From these results it is evident that mesoporous Ta oxides are effective photocatalysts and for this reason may spur a great deal of research interest over the coming years.

## 2.6. Alkali-Metal-Reduced Mesoporous Niobium, Tantalum, and Titanium Materials

Recent work in our group showed that mesoporous Nb, Ta, and Ti oxides can act as stoichiometric electron acceptors and hosts for a variety of electron-donating guest species, thus opening the doorway to a wide variety of reactions involving electron transfer to a mesoporous host lattice. This synthetic approach to achieving populated d states in the walls of the mesostructure differs appreciably from previous approaches in that the introduction of electrons into the d band occurs *after* the mesostructure has been formed. The use of air-sensitive, low-valent transition metal alkoxide precursors, which may well become oxidized during the course of mesostructure formation, can thus be avoided. In our work reduced transition metal molecular sieves<sup>[42]</sup> were obtained by

Table 3. Comparison of the photocatalytic activity of NiO loaded tantalum oxides.

| Tantalum oxides                                            | Loading of NiO [wt %] | BET surface area [m <sup>2</sup> g <sup>-1</sup> ] | H <sub>2</sub> produced [ $\mu\text{mol h}^{-1}$ ] | O <sub>2</sub> produced [ $\mu\text{mol h}^{-1}$ ] |
|------------------------------------------------------------|-----------------------|----------------------------------------------------|----------------------------------------------------|----------------------------------------------------|
| amorphous Ta <sub>2</sub> O <sub>5</sub> <sup>[a]</sup>    | 1.0                   | 145                                                | 46                                                 | 24                                                 |
| treated <sup>[b]</sup>                                     |                       | NA                                                 | 125                                                | 43                                                 |
| orthorhombic Ta <sub>2</sub> O <sub>5</sub> <sup>[a]</sup> | 1.0                   | NA                                                 | 10                                                 | 0                                                  |
| treated <sup>[b]</sup>                                     |                       | NA                                                 | 389                                                | 194                                                |
| mesoporous Ta <sub>2</sub> O <sub>5</sub> <sup>[a]</sup>   | 4.0                   | 370                                                | 150                                                | 73                                                 |
| treated <sup>[b]</sup>                                     |                       | 141                                                | 515                                                | 272                                                |

[a] Crude material. [b] Calcinated template-free material.

treatment of mesoporous Nb oxide with Na/naphthalene in THF (Figure 6B). The reduced materials were gray to black and showed full retention of mesostructure after reduction as determined by XRD and nitrogen adsorption. The XPS spectra showed that the Nb 3d<sub>5/2</sub>, 3d<sub>3/2</sub> emissions shift

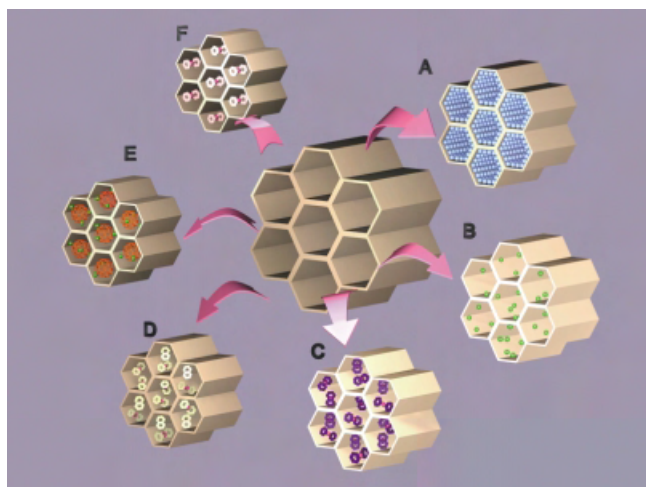


Figure 6. Reduction of mesoporous niobium oxide with: A) bis(toluene) niobium to give a material with low valent Nb on the surface; B) Sodium naphthalene to give a reduced sodium niobate with potential applications as a cathodic material; C) cobaltocene to give a material in which the mesostructure is filled with superparamagnetic molecular ensembles; D) nickelocene to give a mesoporous spin glass; E) K<sub>3</sub>C<sub>60</sub> to give one-dimensional potassium fulleride wires supported by the mesoporous oxide lattice; F) bis(benzene)chromium to give low-dimensional organometallic hole metals in the pores.

monotonically to lower binding energy with increasing reduction from 207.8, 210.6 eV for the unreduced materials to 206.0, 208.8 eV for the sample reduced with 1.0 equivalent of sodium naphthalene. This trend is consistent with a gradual change of the Nb oxidation state from Nb<sup>V</sup> to Nb<sup>IV</sup> as the Na loading level increases. However, the two distinct peaks for the Nb<sup>IV</sup> and Nb<sup>V</sup> were not resolved, possibly because of local electron hopping between sites faster than the XPS time scale. This work was then expanded to include all alkali-metal-reduced mesoporous Nb, Ta, and Ti oxides.<sup>[43]</sup> The order of stability to reduction by alkali metal was found to be Ta > Nb >> Ti as judged by retention of the XRD pattern after reaction. The band gaps for all materials studied ranged from 3.3–4.0 eV and the distance from impurity band, thought to be composed of the transition metal *nd* orbitals [*n* = 3(Ti), 4(Nb), 5(Ta)] and the alkali-metal *ns* orbitals [*n* = 2(Li), 3(Na), 4(K), 5(Rb), 6(Cs)], to conduction band was roughly 2.1 eV as calculated from their UV spectra (Figure 7). Interestingly, all of the alkali-metal-reduced Nb and Ta oxide materials studied were insulating (less than 10<sup>−8</sup> Ω<sup>−1</sup> cm<sup>−1</sup>), while the Li–Ti material gave conductivity values of up to 10<sup>−6</sup> Ω<sup>−1</sup> cm<sup>−1</sup>. The insulating nature of the Ta and Nb materials was attributed to Anderson localization effects, a phenomenon studied in Na-reduced amorphous tungsten oxides Na<sub>x</sub>WO<sub>3</sub>.<sup>[69]</sup> Since the Li–Ti materials are semiconducting, an Anderson transition to a more continuous electronic state may have occurred. The superconducting quantum interference device (SQUID) magnetometry mea-

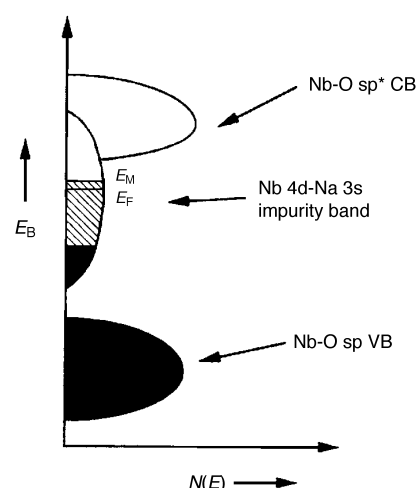


Figure 7. Energy-level diagram of alkali-metal-reduced M-TMS1 (M = Ta, Nb, Ti). The electron from the alkali metal resides in an *nd*(transition metal)-*ns*(alkali metal) impurity band between the valence and conduction bands of the mesostructure. *E<sub>f</sub>* denotes the Fermi level while *E<sub>m</sub>* represents the mobility edge. Black areas represent regions filled with electrons while the area marked by grid lines represents a region of localized states extending down into the (black) filled levels of the impurity band; CB = conduction band, VB = valence band. Reproduced with permission from ref. [43].

surement of all of these materials showed evidence for paramagnetic behavior. The presence of free electrons in the structure was further supported by their electron paramagnetic resonance (EPR) spectra showing one peak typical of a free electron (2.003 g). The electrochemical studies on the unreduced Ti materials give a cyclic voltammogram with two clear peaks at 0.8 V and 1.4 V, which indicate reversible reduction–oxidation of the oxide framework, and hence possible applications in Li batteries. The stoichiometric retention of reductant with almost no loss of porosity gives these oxides a distinct advantage over other porous cathodic materials, which typically undergo a phase change to a non-porous state on addition of more than just a few tenths of an equivalent of alkali metal.<sup>[70]</sup> This improvement is most likely to be the result the greater structural flexibility of the amorphous walls of mesoporous oxides as compared to the more rigid crystalline framework of other cathodic materials. In contrast, the unreduced Nb and Ta materials displayed very weak or no reversible electrochemical reduction–oxidation properties. The strong capacitance in these materials was attributed to charge mobility problems arising from greater electron localization in the Nb and Ta materials than in the Ti materials.

## 2.7. Superparamagnetic Mesoporous Niobium Oxide/ Cobaltocene and Nickelocene Composites

Of special interest is the intercalation of cobaltocene into mesoporous niobium oxide.<sup>[71, 72]</sup> Cobaltocene is a strong reductant and has a rich host–guest inclusion chemistry with many layered materials, such as sulfides and selenides, that can act as electron acceptors.<sup>[73]</sup> Recent work in our group shows that mesoporous Nb oxide readily reacts with cobalt-



ocene to give a dark gray material (Figure 6C) which on increased cobaltocene loading undergoes a dramatic change in magnetic properties from paramagnetic to superparamagnetic behavior, a property which is normally only observed in the nanometer colloid grains of transition metals and their compounds. Interestingly, bulk  $\text{Nb}_2\text{O}_5$  does not react with cobaltocene, which demonstrates that the broader distribution of energy of the d band in the amorphous mesostructure leads to a fraction of states which are low enough in energy to accept an electron from cobaltocene. The materials were characterized by XPS, and displayed Nb  $3d_{5/2}$ ,  $3d_{3/2}$  emissions at 206.8 and 209.6 eV, indicative of slight reduction from  $\text{Nb}^V$  to  $\text{Nb}^{IV}$  state as compared to the starting materials (207.6 and 210.4 eV), and the Co  $2p_{3/2}$  region in the sample prepared with more than 0.5 equivalent of cobaltocene showed two distinct cobalt peaks for cobaltocene and cobaltocinium at 779.7 and 781.1 eV, respectively. The superparamagnetic materials have a Co/Nb molar ratio above a critical value of 0.5:1.0 and SQUID  $\chi$  versus  $T$  measurements show a blocking temperature ( $T_b$ ) of 18 K (Figure 8, curve a), below which the

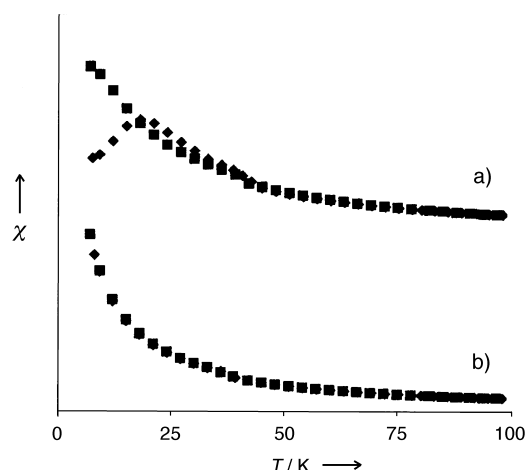


Figure 8. Temperature dependence of magnetic susceptibility for Nb-TMS sample ( $\blacklozenge$  = zero-field cooled with increasing temperature  $\blacksquare$  = with reducing temperature) with a) 0.5 equivalents of cobaltocene showing a superparamagnetic blocking transition ( $T_b$ ) at 22 K; b) 0.4 equivalents of cobaltocene showing no evidence of a superparamagnetic transition.

individual spins in the nanoscale magnetic domains are said to be blocked to certain low-energy transitions because of thermal fluctuations.<sup>[74]</sup> Materials with less cobaltocene were paramagnetic (Figure 8, curve b). The retention of neutral cobaltocene in the structure after the maximum level of cobaltocinium was reached was attributed to a strong host–guest interaction. This was the first reported example of superparamagnetism in a molecular ensemble.

Recently superparamagnetism was also observed in iron oxide based mesostructured surfactant composites,<sup>[75, 76]</sup> and it was attributed to small domains in the walls of the structure, not altogether surprising given that colloidal grains of many Fe-containing materials often display superparamagnetic properties. Since other reduced mesoporous oxides are not superparamagnetic, the origin of cooperative magnetism in this system must be related to the cobaltocene in the pores

and short-range coupling between the unpaired electrons associated with the Co centers. Whether or not the unpaired electrons in the walls of the structure interact with the spins of the Co species is not known at this stage. What makes this system particularly unusual is that bulk cobaltocene is paramagnetic and superparamagnetism is normally observed in small grains of materials which are ferromagnetic in their bulk form.

To investigate the factors contributing to superparamagnetism in this system, a study of variation of pore size, pore wall thickness, and wall composition was conducted.<sup>[72]</sup> The wall thickness and pore sizes were systematically varied from 15–30 Å and the 23–33 Å, respectively, while the composition of the walls was varied from Nb, to Ta, and Ti. SQUID measurements,  $\chi$  versus  $T$  and  $B$  versus  $H$ , were performed for all the materials. In all the materials the mean particle size was estimated from the magnetic data to be about 14 nm.<sup>[77]</sup> The pore size and wall thickness of the mesostructure seemed to have little effect on the magnetic behavior of these materials. The presence of cigar-shaped cobaltocene-based clusters within a single pore rather than spherical regions spanning several pore diameters was invoked to explain the 14 nm domain sizes, since some effect on the magnetic properties of increasing pore-wall thickness would be expected if the pore walls were part of the magnetic domains. The samples synthesized from cobaltocene and Ta-TMS1 or Ti-TMS1 absorbed much lower levels of organometallic reagent, mostly in the nonmagnetic cobaltocinium ion form, and only displayed paramagnetic behavior. The lower levels of cobaltocene absorption were attributed to the lower oxidizing ability of the walls of these materials as compared to the Nb-based structures. Thus, from this study, it is evident that the host material must be reactive enough towards reduction by a guest species to absorb, in a first step, a critical amount of cobaltocene in the cobaltocinium ion form. Once this critical level has been reached the materials absorb more cobaltocene, but this time in the neutral form. Once enough cobaltocene has aggregated in the pores, the materials undergo a transition to superparamagnetic behavior because of an increased density of unpaired electrons in the pore channels.

To investigate the effect of the overall spin of the guest species on the magnetic behavior of the system, we chose to synthesize mesoporous niobium oxide composites of metalocene species with more than one unpaired electron per nucleus.<sup>[78]</sup> Thus, new composite materials were prepared from nickelocene, which has two unpaired electrons per Ni center, and mesoporous niobium oxide (Figure 6D). These materials showed an interesting loading-dependent transition from superparamagnetic (blocking temperature  $T_b$  at 8 K) to spin-glass behavior, a phenomenon normally associated with amorphous metal alloys in which the spins essentially become “frozen” in a random orientation below a certain temperature. These nickel-based composites in general possessed a much lower loading level of organometallic species, as determined by XPS (molar ratio of Ni:Nb was 0.07:1), than the cobalt-based composites. This result was rationalized by the greater number of unpaired electrons in Ni-based materials, that is, the ground state of nickelocene is a triplet

state and its cation is in a doublet state while cobaltocene is in a doublet state and its cation in a singlet state. In a study of magnetic behavior of Fe-doped Pd alloys, a transition from the superparamagnetic state to the spin-glass state was found to occur on increasing the concentration of the magnetically active species in the alloy.<sup>[79]</sup> The transition to the spin-glass state in the nickelocene composites took place at the molar ratio of Ni:Nb in the amount of 0.1:1. Currently we are embarking on a series of more detailed magnetic studies in an effort to elucidate the origin of superparamagnetism and spin-glass behavior in this new family of reduced mesoporous composites.

## 2.8. Low-Dimensional Organometallic Molecular Wires Supported by a Mesoporous Niobium Oxide Host

While late transition metal sandwich complexes form insulating materials with magnetic properties typical of fine particles and amorphous alloys, the analogous early transition metal species ( $[\text{Cp}_2\text{Cr}]$ ,  $[\text{Cp}_2\text{V}]$ ,  $[(\text{C}_6\text{H}_6)_2\text{Cr}]$ ,  $[(\text{C}_6\text{H}_6)_2\text{V}]$ ;  $\text{Cp} = \text{C}_5\text{H}_5$ ) generally form paramagnetic materials (Figure 6F) with conductivity values as high as  $10^{-5} \Omega^{-1}\text{cm}^{-1}$ .<sup>[80]</sup> In these composites, the retention of the mesostructure after all reactions was confirmed by the powder XRD patterns and nitrogen adsorption–desorption isotherms. In the  $[(\text{C}_6\text{H}_6)_2\text{Cr}]$  system, both  $[(\text{C}_6\text{H}_6)_2\text{Cr}]$  and  $[(\text{C}_6\text{H}_6)_2\text{Cr}]^+$  were detected in the pores by XPS and ESR. The Nb oxide walls of the mesostructure showed signs of very slight reduction, consistent with electron transfer from the organometallic species to the host lattice. The conductivity in the Cr- and V-based materials was rationalized by a model where the hole in the mixed oxidation state organometallic phase (introduced by oxidation by the mesostructure) is the charge carrier, since in all the cases studied both cationic and neutral species were required for conductivity, and the reduced mesostructure was previously shown to be insulating. To study the effect of changing the dopant on the conductivity of this new family of materials, bis(benzene)vanadium, vanadocene, and chromocene composites of mesoporous niobium oxide were prepared.<sup>[81]</sup> The conductivity of these materials was  $10^{-4}$ ,  $10^{-5}$ , and  $10^{-6} \Omega^{-1}\text{cm}^{-1}$ , respectively. The mixed oxidation states nature of the organometallic phase in each material was revealed by XPS and EPR which provided concrete evidence for  $[(\text{C}_6\text{H}_6)_2\text{V}]/[(\text{C}_6\text{H}_6)_2\text{V}]^+$ ,  $[\text{Cp}_2\text{V}]/[\text{Cp}_2\text{V}]^{2+}$ , and  $[\text{Cp}_2\text{Cr}]/[\text{Cp}_2\text{Cr}]^+$  in the pores of the respective materials, however, all in levels of less than 0.01 equivalents of total dopant per mole of Nb, almost 50 times less than that in the cobaltocene system, which was completely insulating under the conditions studied. These trends were rationalized by the balance between Hubbard potentials  $U$  and bandwidths  $W$  of the transition metals in question where the hole in the mixed-oxidation-state phase was regarded as the charge carrier in each system.<sup>[82]</sup> Currently we are performing solid-state NMR spectroscopy and variable temperature conductivity studies on these materials to further elucidate their structure and properties. Recent unpublished results in our group have demonstrated that bis(toluenes)niobium acts as an Nb transfer reagent, effectively depositing Nb atoms on the surface of the

mesostructure.<sup>[83]</sup> In this case a mixed-valent organometallic phase it not formed, presumably because of the instability of the bis(toluenes)niobium cation. We are currently investigating the physical properties of this new composite.

## 2.9. One-Dimensional Alkali-Metal Fulleride Wires Supported by a Mesoporous Niobium oxide Host

Another family of electroactive mesoporous transition metal oxide materials recently reported by our group are the mesoporous niobium oxide intercalates of the superconductor  $\text{K}_3\text{C}_{60}$  (Figure 6E).<sup>[84, 85]</sup> Since the electronic properties of alkali-metal fullerides show a strong dependence on the level of reduction,<sup>[86]</sup> an important aspect is that the oxidation state of the fulleride phase in the pores can be easily tuned by the addition of potassium naphthalene. The pore size of the mesoporous niobium oxide host material used in this study was  $22 \text{ \AA}$ , just large enough to accommodate one molecule of  $\text{K}_3\text{C}_{60}$  (unit-cell length ca.  $14 \text{ \AA}$ ) across the diameter of the pore. This feature allows us to investigate the properties of one-dimensional alkali-metal fullerides and the effects of quantum confinement on superconductivity and metallic properties of alkali-metal fullerides in general. The reaction of  $\text{K}_3\text{C}_{60}$  and trimethylsilylated mesoporous niobium oxide in THF solution gave a material with alkali-metal fulleride with an oxidation state of  $n=0.5$  in the pores, as measured by its Raman spectra (for fulleride salts of the type  $\text{M}_n\text{C}_{60}$  ( $\text{M} = \text{K}, \text{Rb}, \text{Cs}$ ), the  $\text{A}_g$  mode shifts roughly  $6 \text{ cm}^{-1}$  for every integer increment in the value of  $n$ ).<sup>[86]</sup> The reduction of the niobium mesostructure by the fulleride was illustrated by XPS spectrum, which indicated a level of reduction equivalent to that obtained by treatment of mesoporous niobium oxide with 0.4 equivalents of potassium naphthalene. The conductivity of this material was  $1.25 \times 10^{-3} \Omega^{-1}\text{cm}^{-1}$ , several orders of magnitude greater than that observed for a sample of fulleride-free mesoporous niobium oxide reduced with 0.4 equivalents of potassium naphthalene. This result suggests that the conductivity pathway in this material is through the fulleride-units on the surface of the material or through the channels, and not through the niobium oxide walls of the structure. When this composite was further reduced by potassium naphthalene back to  $n=3$  state, the conductivity of this new material was lower than  $10^{-7} \Omega^{-1}\text{cm}^{-1}$ . No further reduction of niobium oxide walls of the mesostructure was observed in this process. Neither material showed signs of a  $T_c$  that might indicate a transition to superconducting behavior, which is not altogether unexpected given the strong dependence of superconductivity on structure in solids. EPR studies suggest that the fulleride phase and the free electron in the walls of the mesostructure are behaving as isolated systems. The room-temperature conductivity patterns of these materials confirm calculations that  $\text{K}_3\text{C}_{60}$  should be a Mott–Hubbard insulator because of its half-filled  $t_{1u}$  band<sup>[86]</sup> and that the accidental vacancies in the  $n=3$  state are responsible for the metallic behavior of bulk  $\text{K}_3\text{C}_{60}$ . However, more structural information is necessary before any direct comparisons can be made to the bulk state.

To more fully probe the dependence of room-temperature conductivity on oxidation state of the fulleride in the pores, the parent composite with  $n=0.5$  was reduced in small increments up to  $n=4.5$ , the process was monitored by Raman and XPS. Interestingly, two conductivity maxima at  $n=2.6$  and  $4.1$  were revealed in this system.<sup>[87]</sup> The conductivity of the materials at these two states was  $10^{-4}$  and  $10^{-1} \Omega^{-1} \text{cm}^{-1}$ , respectively. The maximum at  $n=2.6$  provides indirect evidence that the potassium fulleride phases other than  $n=3$  state might be involved in the conductivity in bulk  $\text{K}_3\text{C}_{60}$ . The maximum at  $n=4.1$  is perhaps even more surprising since the room-temperature conductivity of this composite is almost as high as pure  $\text{K}_3\text{C}_{60}$  and the  $n=4$  state is thought to be insulating.

The effects of pore size and wall composition of mesoporous transition metal oxides on the conductivity of the composites were also studied by changing the mesostructure hosts from Nb to Ti and Ta and expanding the pore size to  $32 \text{ \AA}$ , large enough to accommodate two unit cells across a pore rather than only one. The results revealed that the double maximum behavior was general to other porous hosts, however, the differences in the positions of the maxima were too subtle to draw any conclusions. The change in pore size seemed to have little effect, which suggests that a much more dramatic change in pore size might be necessary to affect the electronic properties. An interesting trend that emerged, however, was an increase in the density of states near the Fermi level, as measured by XPS, in all the samples at the transition point to the conductivity maximum at  $n \approx 4.0$ . This observation is consistent with a transition to metallic behavior, possibly involving a favorable overlap between the band structure of the walls and the fulleride phase, although we are currently performing variable-temperature resistivity studies to confirm this hypothesis.

## 2.10. Electroactive Mesoporous Tungsten Oxides

Cheng and co-workers recently reported the syntheses and electrochromic properties of mesoporous tungsten oxide films.<sup>[88]</sup> These materials were prepared by dip-coating using block copolymers as templates, a procedure that was developed by Stucky's group.<sup>[89, 90]</sup> The coating solutions consisted of a mixture of  $\text{WCl}_6$ , anhydrous ethanol, and tri-block polymer  $\text{EO}_{20}\text{PO}_{70}\text{EO}_{20}$  (BASF Pluronic  $\text{P}_{123}$ ), and either solvent extraction or calcination was used to remove the copolymer template. These materials were characterized by thermogravimetric analysis (TGA), XRD, TEM, and nitrogen adsorption-desorption, which gave compositions of  $\text{WO}_{2.94} \cdot 2.8\text{H}_2\text{O} \cdot 0.011\text{P}_{123}$ ,  $\text{WO}_{2.94} \cdot 1.3\text{H}_2\text{O} \cdot 0.001\text{P}_{123}$ ,  $\text{WO}_{2.94} \cdot 0.8\text{H}_2\text{O} \cdot 0.0005\text{P}_{123}$ , and  $\text{WO}_{2.97} \cdot 0.17\text{H}_2\text{O}$  for the as-synthesized, solvent extracted,  $300^\circ\text{C}$  calcined, and  $400^\circ\text{C}$  calcined samples, respectively. The mesostructures possessed fairly regular pore diameters but were not well ordered and generally collapsed at  $400^\circ\text{C}$  during calcination. The BET surface area for the solvent extracted and calcined ( $300^\circ\text{C}$ ) samples were  $155$  and  $135 \text{ m}^2\text{g}^{-1}$ , respectively, and the corresponding average pore sizes were  $50$  and  $45 \text{ \AA}$ .

Voltammetric measurements of the mesoporous tungsten oxide films showed a well-defined anodic peak for the samples calcined at  $300^\circ\text{C}$  and  $400^\circ\text{C}$  and well-behaved electrochemical reversibility after several cycles. The cyclic voltammograms of samples calcined at  $300^\circ\text{C}$  showed the evolution of multiple anodic peaks during the repetitive insertion-desertion scans which could arise from the different types of hydrogen injection sites and/or the high surface area of the films.

The electrochromic properties of mesoporous tungsten oxide were also studied. The optical change observed for the sample calcined at  $300^\circ\text{C}$ , or for a sample extracted by ethanol during the voltammetric sweep, was completely reversible (Figure 9), while tungsten oxide samples with low surface

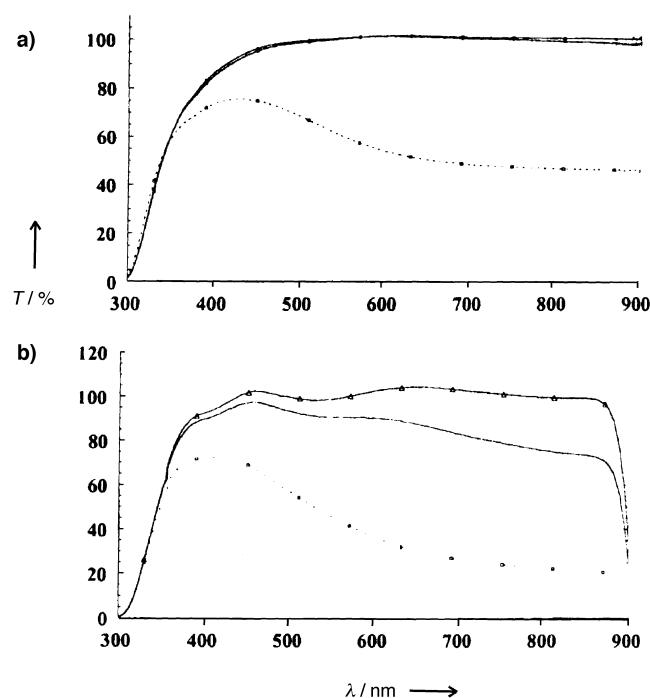


Figure 9. Optical transmittance spectra for a) mesoporous and b) sol-gel tungsten oxide films heated at  $300 \text{ K}$ .  $\Delta$  = initial; — =  $+0.8 \text{ V}$  (1st charge);  $\cdots$  =  $-0.8 \text{ V}$  (1st discharge). Reproduced with permission from ref. [88].

areas, such as a sol-gel derived non-mesoporous film heated at  $300^\circ\text{C}$ , and the same sample heated at  $400^\circ\text{C}$  showed an irreversible coloration/bleaching process. This result was further confirmed by the plots of transmittance variation at  $650 \text{ nm}$  as a function of time, the data were obtained for the transient absorption response to the voltage step. The coloration efficiency (CE) for mesoporous tungsten oxide film calcined at  $300^\circ\text{C}$  was  $21.2 \text{ cm}^2\text{C}^{-1}$  for the first cycle. The chronoamperometric measurements for voltage steps between  $-0.8 \text{ V}$  and  $+0.8 \text{ V}$  (vs. SCE (saturated calomel electrode)) showed the mesoporous films possess better electrochemical stability than the sol-gel nonporous film. Therefore, the high surface area resulting from the mesoporosity of the tungsten oxide films provides enhanced electrochemical and electrochromic properties.

### 3. Mesostructured Sulfides and Selenides

#### 3.1. Mesostructured Germanium Sulfides

Because of their anticipated electronic and optical properties and affinities for heavy metals, researchers have recently been investigating the synthesis and potential applications of mesostructured sulfides and selenides. Ozin's group recently reported a new family of surfactant-templated metal germanium sulfide materials with structures similar to that of as-synthesized MCM-41.<sup>[41, 91]</sup> Various groups have reported mesostructured chalcogenide composites, such as CdS,<sup>[92–94]</sup> ZnS,<sup>[95]</sup> SnS<sub>2</sub>,<sup>[96]</sup> GeS<sub>2</sub>,<sup>[97]</sup> and CdSe.<sup>[98]</sup> The representative synthetic strategy was developed by Stupp and co-workers. This method involves passing H<sub>2</sub>S or H<sub>2</sub>Se over a hexagonal mesophase containing the ether C<sub>18</sub>H<sub>35</sub>(OCH<sub>2</sub>CH<sub>2</sub>)<sub>10</sub>OH, water, and Cd<sup>II</sup> or Zn<sup>II</sup> salts. In contrast, the mesostructured metal germanium sulfides synthesized in Ozin's group were prepared by a non-aqueous surfactant-templating assembly of adamantanoid [Ge<sub>4</sub>S<sub>10</sub>]<sup>4−</sup> cluster precursors in formamide, where (TMA)<sub>4</sub>Ge<sub>4</sub>S<sub>10</sub> (TMA = tetramethylammonium) was used as the inorganic precursor and C<sub>*n*</sub>H<sub>2*n*+1</sub>NMe<sub>3</sub><sup>+</sup>X<sup>−</sup> (*n* = 12, 14, 16, 18, and X = Cl<sup>−</sup>, Br<sup>−</sup>) were used as structure-directing agents (Figure 10). Transition metal cations such as Co<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup>, or Cu<sup>+</sup> were employed as charge-balancing and inorganic framework-chain-linking ions to create well-ordered hexagonal mesostructures.

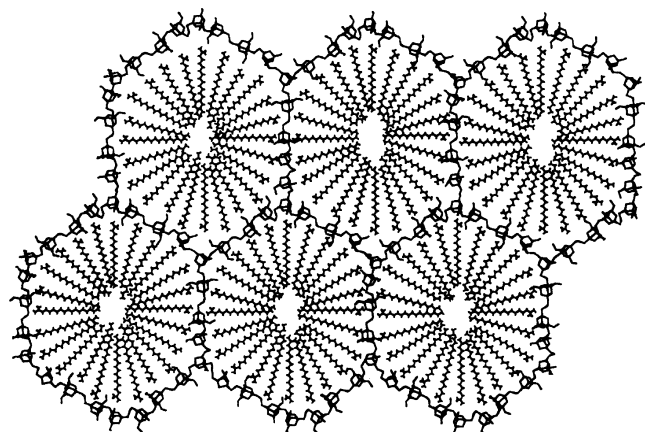


Figure 10. Proposed architecture of a mesostructured germanium sulfide material. (TMA)<sub>4</sub>[Ge<sub>4</sub>S<sub>10</sub>] and (CTA)Br were dissolved in formamide to give a viscous mesophase of the adamantoid clusters charge balanced by surfactant. On addition of a metal salt, the adamantoid clusters link to form a supramolecular, hexagonal, mesostructured material in which the adamantoid clusters are linked by metal ions in the structure.

The powder XRD patterns and TEM images of these materials illustrated a moderate degree of mesostructural order with wormlike morphologies and hexagonal unit cells (Figure 11). The Raman spectra of the mesostructured materials showed overlapping peaks between 240 and 320 cm<sup>−1</sup> for the Zn–S stretching modes, which confirms the presence of metal-linked adamantanoid clusters in the material. The solid-state <sup>1</sup>H (MAS) NMR spectra and cross-polarization (CP) <sup>13</sup>C (MAS) NMR spectra confirmed the presence of the surfactant in the materials, as did TGA and



Figure 11. TEM images of wormlike particles of (CTA)NiGe<sub>4</sub>S<sub>10</sub>. A magnified view of the particle in (right) confirmed that the channels of the material run parallel to the longitudinal axis of the faceted shape. Reproduced with permission from ref. [91].

pyrolysis mass spectrometry. No sulfur-containing small molecules, such as H<sub>2</sub>S, HSMe, and Me<sub>2</sub>S, were detected in the mass spectra. The elemental analyses gave (CTA)<sub>2</sub>M<sub>2</sub>–Ge<sub>4</sub>S<sub>10</sub> with 3–10 wt% unaccounted mass for most of the samples. Only 40% of the surfactant in the materials could be removed by acetone extraction, which indicates that the cationic surfactants (CTA) were functioning as charge-balancing reagents for the anionic framework as well as space-fillers to reinforce the mesostructure. A liquid-crystal templating mechanism was proposed to rationalize the formation of these materials. In this mechanism the terminal negative sulfide groups of the adamantanoid clusters in the initially formed micellar and cylindrical liquid crystalline phase by [Ge<sub>4</sub>S<sub>10</sub>]<sup>4−</sup>, TMA<sup>+</sup>, and surfactant cations could rapidly coordinate to the transition metal species to form a hexagonal mesostructured network. Because of the well-defined nature of the crystalline units in the walls of these materials, it is anticipated that numerous electronic and optical applications, in which a well-defined wall-structure is an advantage, may be possible.

#### 3.2. More Germanium Sulfides and Selenides and Even Some Tin

At about the same time the non-aqueous synthesis of mesostructured metal germanium sulfides from [Ge<sub>4</sub>S<sub>10</sub>]<sup>4−</sup> clusters was being developed by Ozin's group, Kanatzidis and co-workers were working on the synthesis of related mesostructured metal germanium sulfides and selenides, (C<sub>*n*</sub>H<sub>2*n*+1</sub>NMe<sub>3</sub>)<sub>2</sub>[MGe<sub>4</sub>Q<sub>10</sub>], where Q = S and Se, M = Zn, Cd, Hg, Ni, and Co, *n* = 12, 14, 16, 18,<sup>[40, 99]</sup> using a mainly aqueous route (with a small amount of ethanol and methanol). Certain aspects of the synthetic method, chemical formula, overall three-dimensional framework organization, and thermal stability of the materials are different from those reported by the Ozin group. The method developed by Kanatzidis and co-workers involves the stoichiometric metathesis reactions between [Ge<sub>4</sub>Q<sub>10</sub>]<sup>4−</sup> (Q = S, Se) anions and metal dichlorides in the presence of long-chain cationic surfactants at 20–80 °C. The charge on the [Ge<sub>4</sub>Q<sub>10</sub>]<sup>4−</sup> cluster was balanced by one M<sup>2+</sup> and two surfactant RNMe<sub>3</sub><sup>+</sup> ions. Energy dispersive microprobe analysis (EDS) on the resulting material gave the chemical formula (RNMe<sub>3</sub>)<sub>2</sub>[MGe<sub>4</sub>Q<sub>10</sub>], slightly different from the formula of the materials synthesized by the Ozin group.<sup>[41]</sup> The powder XRD patterns, high resolution (HR) TEM images and atom pair distribution function (PDF) plots of these materials revealed a mesostruc-

tured nature with short-range local order and nonperiodic disordered wall structure much like that of mesoporous silica MSU-1, MSU 2, and MSU 3.<sup>[100]</sup> The surfactant-filled inorganic framework pores were composed of adamantanoid  $[\text{Ge}_4\text{Q}_{10}]^{4-}$  clusters with linking tetrahedral divalent transition metal ions, and organized in a worm-hole pattern with a constant average tunnel to tunnel distance (Figure 12). The pore size could be tuned from 30 to 45 Å by varying the

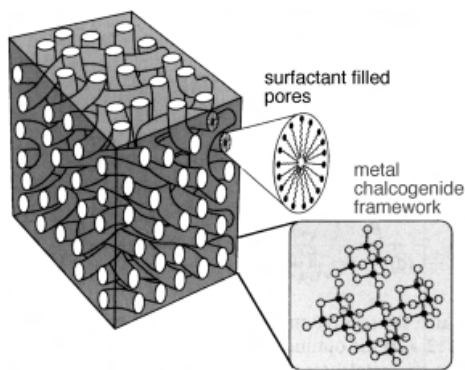


Figure 12. Proposed structure model of the  $\text{C}_n\text{MGeQ}$  phases. The amorphous framework is perforated by the wormhole-like micelles of surfactant molecules.

surfactant chain length and the overall structure of the  $[\text{MGe}_4\text{Q}_{10}]^{2-}$  framework. The Raman and IR spectra of these materials showed that the adamantanoid clusters remained intact and gave evidence for additional M–Q bonds present. All materials were wide band gap semiconductors in the energy range of 1.0–3.6 eV and the band gaps were independent of the surfactant chain length. Based on the TGA, about 70–80 % of surfactant inside the inorganic framework could be removed without collapse of the mesostructure by heating at about 180–220 °C under vacuum for 3–4 days.

Materials containing the divalent  $\text{Mn}^{2+}$  ion behaved differently and did not lead to an immediate precipitation in either the non-aqueous or aqueous mediums described above. This problem was resolved by conducting the reaction of  $\text{Na}_4\text{Ge}_4\text{S}_{10}$ ,  $\text{MnCl}_2$ , and mesityltrimethyl ammonium bromide in a stoichiometric ratio under hydrothermal conditions.<sup>[101]</sup> This method resulted in new hexagonally ordered mesostructures of metal germanium sulfides with only short-range local order similar to those reported by Ozin's group. The semiconducting properties of this material were confirmed by solid-state absorption spectra, giving a band gap of 2.84 eV.

Trivalent cations, such as  $\text{Ga}^{3+}$  and  $\text{In}^{3+}$ , can also act as the cluster-linking agents in these materials, which leads to light-emitting mesostructured sulfides with hexagonal order.<sup>[102]</sup> The mesostructure of these two materials were similar to their divalent counterparts and the optical absorption confirmed their semiconducting behavior. The chemical formula of both materials was close to  $(\text{CP})_2\text{M}_{1.5}\text{Ge}_4\text{S}_{11}$  (CP = cetylpyridinium,  $\text{M} = \text{Ga}^{3+}$ ,  $\text{In}^{3+}$ ), indicative of a very high metal content which could not be accounted for by the charge balance between surfactant, metal cations, and cluster anions, possibly because of the presence of  $\text{S}^{2-}$  species. A unique feature of these two materials was the intense photoluminescence observed when excited with light energy above their

band gaps. For example, under an excitation light of 3.35 eV (370 nm) at 77 K, an intense green emission with a maximum 2.35 eV (528 nm) and 2.32 eV (535 nm) was observed for  $\text{CPGaGeS}$  and  $\text{CPInGeS}$ , respectively (Figure 13). The optoelectronic property possibly originates from the pyridinium chromophore of the surfactant. This was the first observation of light emission from mesostructured metal thiogermanates.

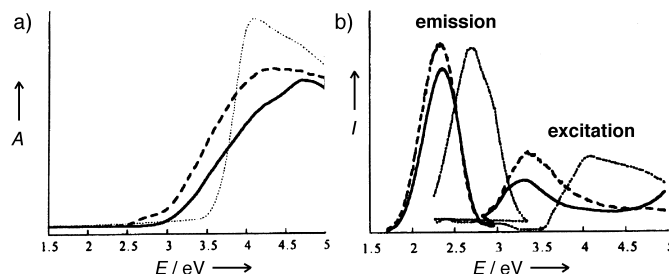


Figure 13. a) Electronic absorption spectra of mesostructured sulfides. b) Photoluminescence and excitation spectra of the same materials (—:  $\text{CPGaGeS}$ ; ---:  $\text{CPInGeS}$ ; .....:  $\text{CPBr}$ ). Reproduced with permission from ref. [102].

This methodology of supramolecular assembly of chalcogenide nanocomposites could be expanded to synthesize stable binary systems including  $[\text{Fe}_4\text{S}_4]$  and  $[\text{Ge}_4\text{Q}_{10}]^{4-}$  ( $\text{Q} = \text{S}$ ,  $\text{Se}$ ) clusters as building blocks for the inorganic frameworks.<sup>[103]</sup> The cluster  $[\text{Fe}_4\text{S}_4]$  was selected as a research target because it is important in biological systems, and provides a major part of the foundation for electron transfer, catalytic, and enzymatic processes in living organisms.<sup>[104]</sup> This material possessed hexagonal mesoscopic order and was prepared in the non-aqueous solvent mixture of formamide and dimethyl formamide (DMF). This general method has opened a doorway for preparing a stable hybrid system with multiple functionality.

Another new class of mesostructured selenide semiconductors with an open framework based on tetrahedral  $[\text{SnSe}_4]^{4-}$  ion was reported recently by the Kanatzidis group.<sup>[105]</sup> These materials are important not only because of their interesting electronic properties but also because of their varied pore organization, which includes disordered worm-hole, hexagonal, and even cubic phases. It was known that  $[\text{SnSe}_4]^{4-}$  possessed the same tetrahedral structure as  $[\text{SiO}_4]^{4-}$  and that it was smaller and heavier than the  $[\text{Ge}_4\text{Q}_{10}]^{4-}$  ( $\text{Q} = \text{S}$ ,  $\text{Se}$ ) clusters. Therefore, it was expected that a similar topological structure to silicas and semiconductors with narrower band gaps than metal germanium chalcogenides would be obtained. These materials were made by spatially controlled assembly of  $[\text{SnSe}_4]^{4-}$  ions in formamide with various divalent metals such as  $\text{Mn}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ , and  $\text{Hg}^{2+}$  in the presence of cetylpyridinium surfactant as the template. Their general chemical formula were described as  $(\text{CP})_{4-2x}\text{M}_x\text{SnSe}_4$  (where  $1.0 < x < 1.3$ ). XRD patterns and TEM images revealed that, under the same experimental conditions, all the materials had hexagonal mesostructures such as silica MCM-41 except the Zn analogue, which had a cubic mesostructure such as MCM-48. The structure of the Zn materials was dependent on the surfactant concentration. When the concentration was reduced by 50 %, the product had an hexagonally ordered

mesophase with uniform pore size. The presence of the tetrahedral  $[\text{SnSe}_4]^{4-}$  ion clusters was demonstrated by  $^{119}\text{Sn}$  Mössbauer spectroscopy. The UV-visible/near-IR spectroscopy showed the band-gap transition in the energy range of 1.4–2.4 eV, values similar to those of CdTe (1.45 eV) and GaAs (1.54 eV) semiconductors. In summary, while these materials are not yet completely stable to template removal, their fascinating array of ordered structures and unusual optoelectronic properties may lead to applications in which accessible internal void-space porosity is not a requirement.

## 4. Mesostructured Metals

### 4.1. Mesostructured Platinum

Because of the importance of zero-valent transition metals in many catalytic processes the synthesis of nanostructured metals with high surface areas and controlled porosity represents a significant challenge for materials scientists. In 1997 Attard and co-workers reported the aqueous syntheses of mesostructured metallic platinum by surfactant liquid crystal templating.<sup>[106]</sup> In this work, hexachloroplatinum acid ( $\text{H}_2\text{PtCl}_6$ ) and ammonium tetrachloroplatinate  $[(\text{NH}_4)_2\text{PtCl}_4]$  were employed as the metal source and octaethyleneglycol monohexadecyl ether  $\text{C}_{16}(\text{EO})_8$  as the hexagonal structure-directing agent. To obtain mesostructured platinum metal, pure Fe, Zn, Hg, or hydrazine hydrate, were used in situ as reducing agents after the self-assembly processes for the system  $\text{H}_2\text{PtCl}_6$  and  $[(\text{NH}_4)_2\text{PtCl}_4]$ , respectively. The surfactant template, metal residues, and small molecules were removed by repetitive washes with acetone, water, and hydrochloric acid until TGA showed almost no further weight loss at up to 600 °C in air. SEM images revealed that the materials were composed of particles 90–500 nm in diameter, and TEM showed evidence of small grains possessing a hexagonal mesostructure with a pore diameter of 30 Å and a pore wall thickness of 30 Å (Figure 14). These results were consistent with the broad and poorly defined XRD pattern, indicative of either small domains of hexagonal order or large amorphous regions in the sample. The extended X-ray absorption fine structure (EXAFS) data obtained for the platinum  $\text{L}_{\text{III}}$  edge of the materials were in good agreement with the presence of pure platinum metal and no oxygen backscattering shells were found. The amplitude of the EXAFS spectrum and the corresponding coordination number of mesoporous platinum were lower than those of bulk metallic platinum (also revealed by EXAFS) could be attributed to high surface area for the mesoporous materials, although no nitrogen adsorption data was reported. In a subsequent paper, this technique was extended to the synthesis of thin films,<sup>[107]</sup> and nitrogen adsorption studies revealed surface areas of 23 m<sup>2</sup>g<sup>−1</sup>, comparable to that of colloidal Pt. The proposed mechanism of mesostructure formation in this new class of materials involved stabilized metal precursors at the interface between the hydrophobic and hydrophilic domains of the microphase-separated environment. Then the fast reduction of the platinum salts yielded

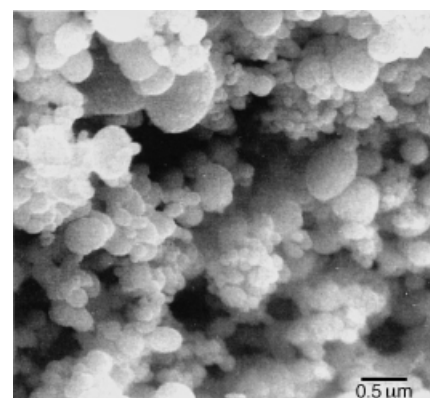


Figure 14. SEM image of a washed sample of mesoporous platinum (top) and TEM image of  $\text{H}_1$ -platinum (bottom). The material was suspended in acetone, sonicated for 5 min. and applied to a carbon-coated copper grid.<sup>[106]</sup>

small colloidal primary metallic particles on the interface followed by agglomeration and coalescence until the walls become homogeneous. This interesting new method has recently been extended to liquid crystal template syntheses of Ru/Pt alloys<sup>[108]</sup> and shows promise as a general method towards mesostructured metallic materials which may find applications in catalytic hydrogenation and fuel-cell design.

### 4.2. Metal Carbonyl Compounds as Mesostructure Building Blocks

In 1998, we attempted the synthesis of mesoporous Pt using metal carbonyl anions and cationic surfactants as building blocks with thermal or photolytic decomposition of the resulting self-assembled platinum carbonyl surfactant phases required to eliminate the carbon monoxide and leave behind the pure metal mesostructure.<sup>[109]</sup> While this work resulted only in the formation of layered phases, it is included in this review because of the novelty and potential promise of this new synthetic method. Ionic metal carbonyl clusters ( $\text{Na}_2\text{[Pt}_n(\text{CO})_6]_n$ ,  $n = 3\text{--}5$ ) were selected as building blocks because of the great flexibility of composition, size, average charge per Pt atom, and the relative ease of thermal decomposition to the pure metallic state. Trimethyl ammonium surfactants were employed as structure directing agents (Figure 15).

The interdigitated layered structure of these materials was revealed by XRD. The layered structure was further confirmed by TEM images, which showed small regions of local order. Changes in the metal-to-surfactant ratio, brought about

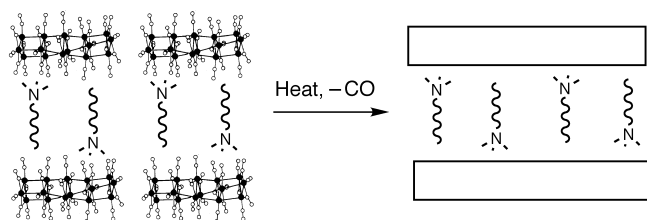


Figure 15. Thermal treatment of layered platinum carbonyl phases results in loss of CO and formation of a new platinum-based layered material.<sup>[109]</sup>

by simply changing the size of the metal carbonyl cluster, or precipitation directly from cold methanol without the addition of degassed water, had no effect on changing the nature of the layered mesophase. Thus no hexagonal or cubic phases were observed. Elimination of CO from the as-synthesized materials by heating at 70 °C under dynamic vacuum resulted in the retention of the structure with only a slight shrinkage of the interlayer spacing with  $d(100)$  going from 19.6 Å to 19.1 Å. The lack of regularly spaced gaps between the platinum units within each layer suggested that the individual platinum clusters had condensed together or that the gaps were too small to be observed. The elemental analyses and  $^{13}\text{C}$  (MAS) NMR spectra confirmed the presence of surfactant in this material. No platinum oxide was observed by energy dispersive X-ray spectra (EDS). Further heating of this material at 120 °C for two days led to loss of the layered structure and formation of an amorphous phase. While only layered materials were formed, this study demonstrated that metal carbonyl anions could be used as precursors to pseudo metallic phases, the loss of CO and condensation of the walls on thermal or photolytic treatment being related to the loss of water and formation of metal–oxygen bridges in the sol–gel synthesis of metal oxides.

## 5. Summary and Outlook

From the contents of this review it is clear that the area of mesoporous non-silica materials has expanded significantly in the last several years and that real-world applications of these exciting materials may not be too far off. By offering controlled porosity, large accessible internal surface areas and void space, in combination with the variable oxidation states of transition metals or semiconducting behavior of sulfides and selenides, this class of materials possess many crucial properties that hitherto have not been possible in zeolites or mesoporous silicates. Already functional materials in this class have been developed for use in photocatalysis, fuel cells, catalytic oxidation, and reduction, while many other applications are no doubt forthcoming. Moreover, the propensity for mesoporous transition metal oxides to act as stoichiometric electron acceptors, which makes them obvious candidates for cathodic materials, has allowed for the exploration of new one-dimensional hole-doped molecular metals with unusual electronic and magnetic properties not observed in the bulk state of these materials, while the optoelectronic activity of narrow band gap selenides and sulfides may lead to development of improved materials for light-harvesting devices. Since this area of porous materials is still in

its infancy it is clear that we are only witnessing the beginning of what has already developed into one of the most active and exciting areas of materials science.

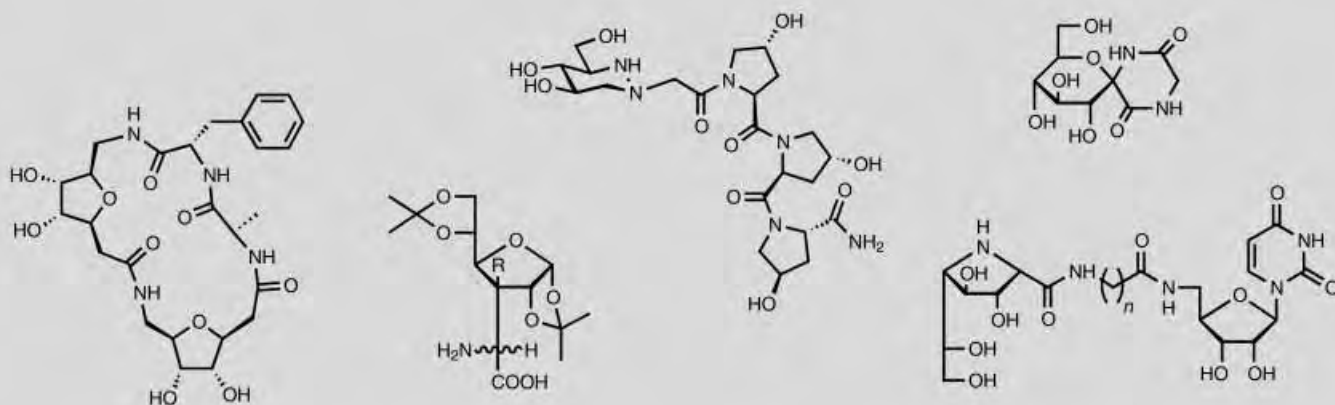
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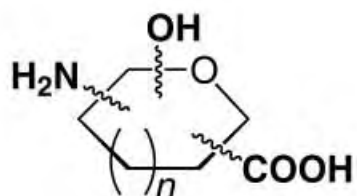
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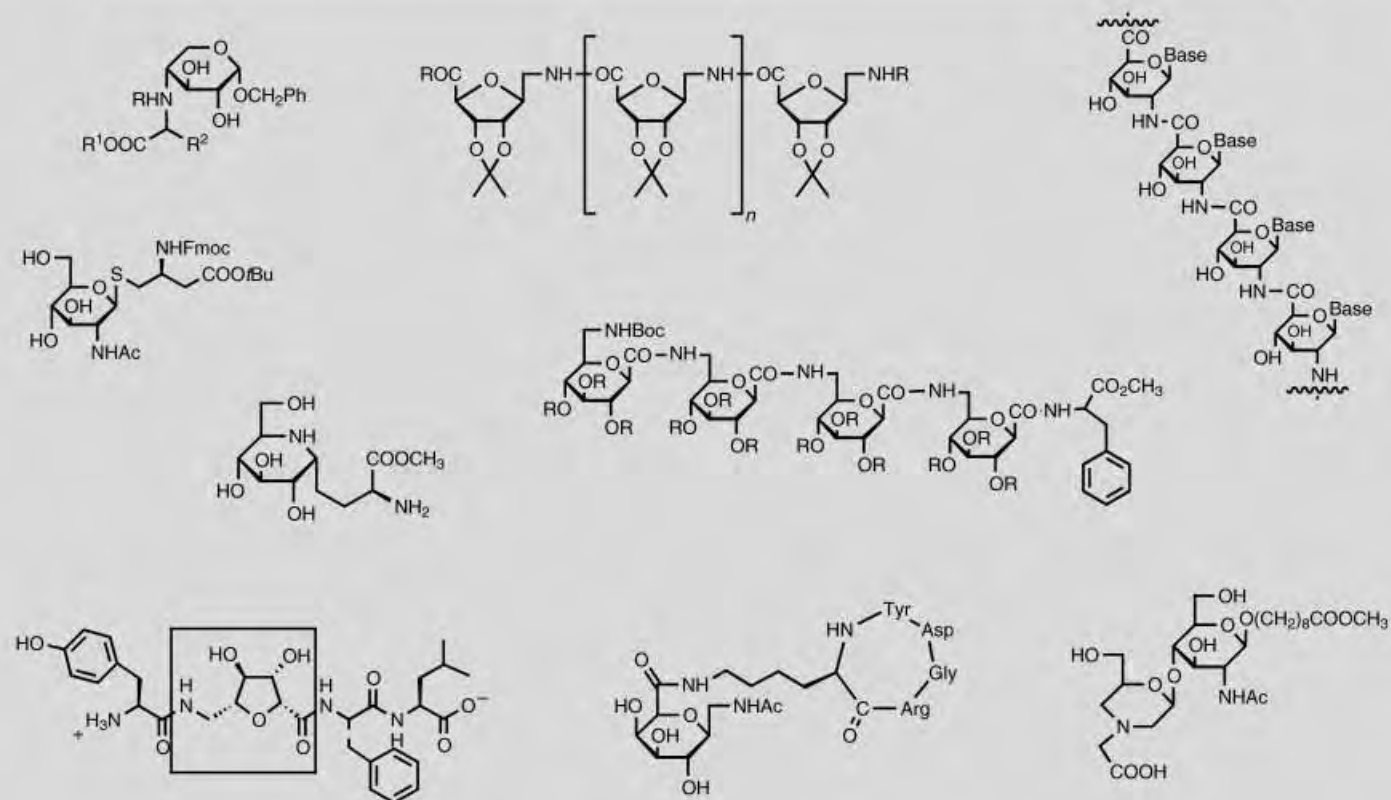
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## sugar–amino acid hybrids



glycomimetics  
peptidomimetics  
biopolymers  
combinatorial chemistry



# Glycosamino Acids: Building Blocks for Combinatorial Synthesis—Implications for Drug Discovery

Frank Schweizer\*

The unique functions of carbohydrates, including energy storage, transport, modulation of protein function, intercellular adhesion, signal transduction, malignant transformation, and viral and bacterial cell–surface recognition, underlie a significant pharmaceutical potential. The development of combinatorial carbohydrate libraries in this important arena has been slow, in contrast to the rapid development of combinatorial synthesis in the area of small-molecule libraries and biopolymers. This is largely as a result of the inherent difficulties presented by this class of polyfunctional compounds. Nevertheless, strategies to cope with these problems have been devised over

the past seven years, and combinatorial carbohydrate libraries have appeared. The incorporation of an amino acid moiety into the carbohydrate scaffold generates glycosamino acids, which are attractive building blocks for the preparation of carbohydrate-based libraries because of the well-established automated peptide synthesis. Derivatization as well as homo- and heterooligomerization of glycosamino acids can be used to create novel structures with unique properties. Glycosamino acids are hybrid structures of carbohydrates and amino acids which can be utilized to generate potential glycomimetics and peptidomimetics. The incorporation of glycosamino acids into pep-

tides allows the engineering of carbohydrate-binding sites into synthetic polypeptides, which may also influence the pharmacokinetic and dynamic properties of the peptides. Furthermore, sugar–amino acid hybrids offer a tremendous structural and functional diversity, which is largely unexplored and requires combinatorial strategies for efficient exploitation. This article provides an overview of previous work on glycosamino acids and discusses their use in combinatorial synthesis and drug discovery.

**Keywords:** combinatorial chemistry • glycoconjugates • glycomimetics • peptidomimetics • sugar amino acids

## 1. Introduction

Amino acids and carbohydrates are two major building blocks used to generate diversity in nature. The ability of amino acids ( $\alpha, \beta, \dots$ ) to form secondary structures in proteins and polypeptides forms the basis of three-dimensional molecular architecture. Carbohydrates present in nucleotides, glycopeptides, and glycolipids communicate with their inter- and intracellular environment through a multitude of molecular interactions. Many of these recognition phenomena are involved in events such as metastasis, infection, and inflammation and have become the subject of intensive medical

research. Glycosamino acids (GAAs) are molecules that combine the structural features of simple amino acids (amino and carboxylic acid functions) with those of simple carbohydrates (cyclic polyols, which may contain additional acetamido or amino functions).<sup>[1]</sup> The resulting hybrid is a highly substituted polyfunctionalized building block, which can be used for the synthesis of compound libraries by means of combinatorial synthesis.

Amino acid building blocks have been widely used for the synthesis of polyamide and small-molecule libraries.<sup>[2]</sup> In contrast to amino acids, GAAs are (poly)hydroxylated amino acids in which additional derivatization of the polyol can lead to increased diversity. GAAs can be derivatized and oligomerized into compound libraries through well-established automated peptide protocols. This approach is particularly attractive in the preparation of glycomimetic libraries, since oligosaccharide library synthesis has not yet reached the same level of automation as peptide synthesis. On the other hand, the engineering of an amino acid moiety into the sugar skeleton enables the GAA to be incorporated into short peptide sequences, thus opening the door to novel peptidomimetics. Additional hydroxy derivatization of the polyol

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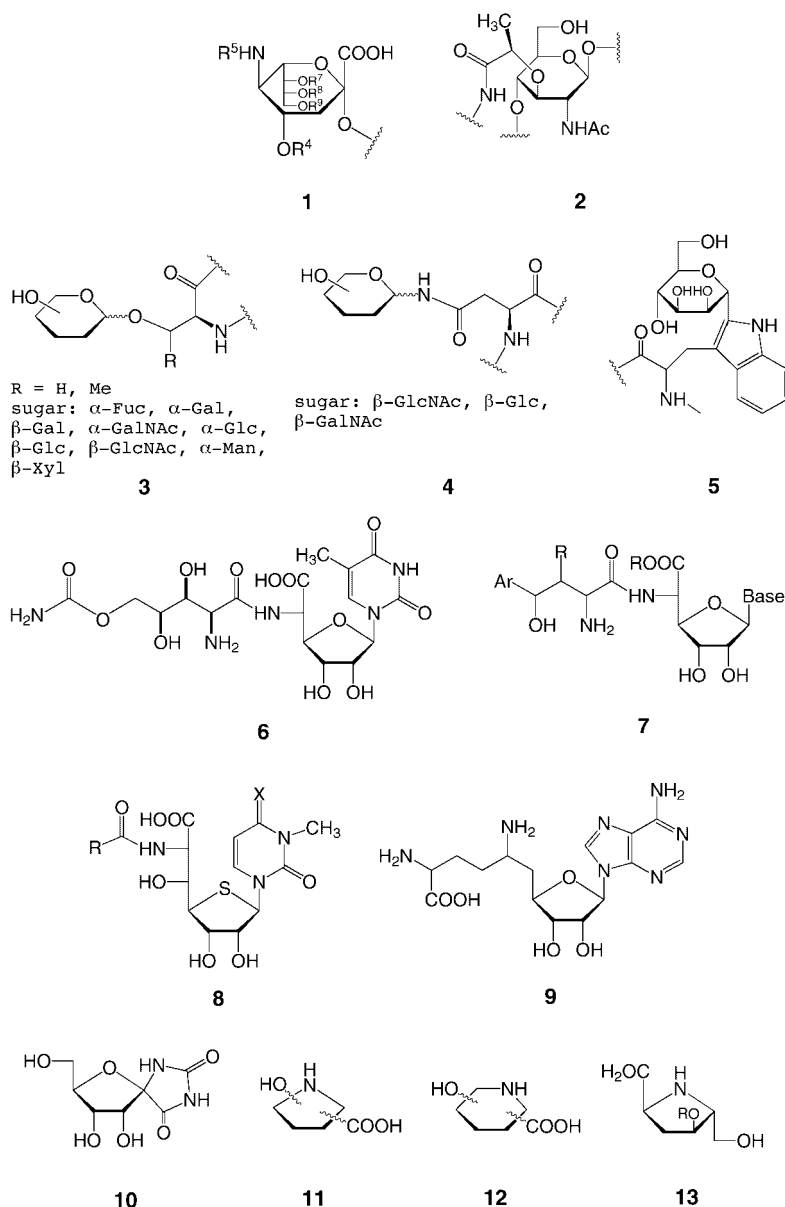
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could increase the lipophilicity of the GAAs and render them likely to permeate cell membranes. Finally, the rich stereochemistry and the high degree of functionalization of GAAs allows them to be used as multivalent scaffolds or platforms for projecting pharmacophore groups. This article presents an overview of previous work on GAAs and discusses their use as building blocks for combinatorial synthesis as well as their implications for drug discovery. A referenced index of approximately 280 previously synthesized GAA structures is provided in Table 1 and Tables 1–19 in the Supporting Information.

## 2. Natural Occurrence

GAAs and their derivatives occur in nature in various forms. For example, the  $\delta$ -GAA sialic acid (**1**) is found in all living organisms, with the exception of certain bacteria. Many inter- and intracellular molecular recognition events depend on sialic acid residues. In the course of an infection, bacteria and viruses recognize sialic-acid-containing structures on the cell surface as adhesion receptors. So far, over 40 different naturally occurring sialic acids have been identified which are partially O- and N-substituted (O-methyl, -sulfate, -acetyl, -phosphate, N-glycolyl, or free amine). Muramic acid (**2**; 2-amino-2-deoxy-3-O-D-lactyl-D-glucose) occurs in bacterial polysaccharides and, in the form of UDP-*N*-acetylmuramyl pentapeptide, is involved in the synthesis of the peptidoglycan. Modified muramyl peptides have been the subject of intensive research over the last 25 years owing to their involvement in the synthesis of the bacterial cell wall.<sup>[3]</sup> GAAs **3** and **4** are components of O- and N-linked glycoproteins and glycopeptides. Other naturally occurring GAAs linked to proteins are cystine-linked glycoproteins<sup>[4, 5]</sup> and the recently identified C-linked mannopyranosyl-L-tryptophan **5**.<sup>[6, 7]</sup> The GAA-based peptidyl nucleoside antibiotic polyoxin (**6**) mimics UDP-*N*-acetylglucosamine, a substrate of chitin synthase, which catalyzes the



final step in the biosynthesis of chitin, an essential component of fungal cell walls.<sup>[8]</sup> Other peptidyl nucleoside antibiotics include the nikkomycins **7**,<sup>[8]</sup> the albomycins **8**,<sup>[8, 9]</sup> and sinefungin (**9**).<sup>[8]</sup> The  $\alpha,\alpha$ -disubstituted hydantoin derivative



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Table 1. Index of previously synthesized A<sub>0</sub>–A<sub>5</sub> GAAs.

| GAA structure | GAA type <sup>[a]</sup> | Table <sup>[b]</sup> | Number of examples | GAA structure | GAA type <sup>[a]</sup> | Table <sup>[b]</sup> | Number of examples |
|---------------|-------------------------|----------------------|--------------------|---------------|-------------------------|----------------------|--------------------|
|               | A <sub>0</sub>          | 1                    | 38                 |               | A <sub>1</sub>          | 10                   | 1                  |
|               | A <sub>0</sub>          | 2                    | 21                 |               | A <sub>2</sub>          | 11                   | 13                 |
|               | A <sub>1</sub>          | 3                    | 14                 |               | A <sub>2</sub>          | 12                   | 3                  |
|               | A <sub>1</sub>          | 4                    | 7                  |               | A <sub>2</sub>          | 13                   | 15                 |
|               | A <sub>1</sub>          | 5                    | 2                  |               | A <sub>2</sub>          | 14                   | 6                  |
|               | A <sub>1</sub>          | 5                    | 13                 |               | A <sub>3</sub>          | 15                   | 17                 |
|               | A <sub>1</sub>          | 6                    | 17                 |               | A <sub>3</sub>          | 16                   | 11                 |
|               | A <sub>1</sub>          | 7                    | 11                 |               | A <sub>4</sub>          | 17                   | 27                 |
|               | A <sub>1</sub>          | 8                    | 7                  |               | A <sub>5</sub>          | 18                   | 9                  |
|               | A <sub>1</sub>          | 9                    | 14                 |               | A <sub>5</sub>          | 19                   | 25                 |
|               | A <sub>1</sub>          | 10                   | 10                 |               |                         |                      |                    |

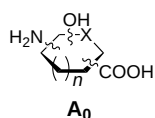
[a] see Scheme 1. [b] Tables 1–19, which contain approximately 280 GAA-based structures, can be found in the Supporting Information.

**10**<sup>[10]</sup> also contains a GAA substructure. Hydantoin derivative **10** shows potent selective antiherbal activity with no toxicity to microorganisms and animals. Replacement of the endocyclic oxygen atom in the pyranose with a nitrogen atom leads to azasugar-based GAAs found in hydroxylated prolines **11**, pipecolic acids **12**, and the antibacterial bulgicine (**13**).<sup>[11]</sup> Hydroxylated prolines have been shown to influence secondary structures in peptides significantly.<sup>[12]</sup> Other antibiotics with a GAA moiety include chrysandin,<sup>[13]</sup> amipurimycin,<sup>[14]</sup> miharamycin,<sup>[15]</sup> gougerotin,<sup>[16]</sup> blasticidin,<sup>[17]</sup> bagougeramine,<sup>[18]</sup> and aezomycin,<sup>[19]</sup> as well as the glycopeptide antibiotics A40926a, b.<sup>[20]</sup>

### 3. Classification of GAAs

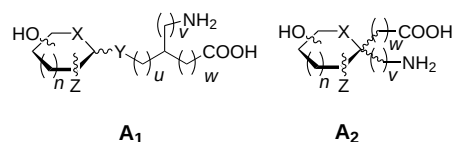
GAAs may be classified into five groups, depending on the position of the amino acid moiety on the cyclic polyol (Scheme 1). The amino acid moiety may either be incorporated directly into a sugar-derived 5- or 6-membered ring, as in the sugar amino acids (SAAs) (A<sub>0</sub> type), or tethered to the sugar ring, as in structures A<sub>1</sub>–A<sub>4</sub> (Scheme 1). The A<sub>1</sub> GAAs or the double-substituted A<sub>2</sub> GAAs are formed by linking the amino acid moiety adjacent to the endocyclic heteroatom. In the branched A<sub>3</sub> and A<sub>4</sub> GAAs, the amino acid moiety is linked further away from the endocyclic heteroatom. Finally,

amino acid moiety is incorporated into the regular sugar frame



(sugar amino acid (SAA))

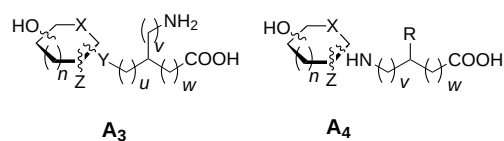
amino acid moiety is tethered to the carbohydrate adjacent to heteroatom X



(glycosyl amino acid)

(double substituted glycosyl amino acid)

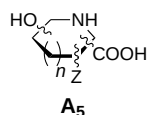
amino acid moiety is tethered to the carbohydrate not adjacent to heteroatom X



A<sub>3</sub>

A<sub>4</sub>

azasugar-based GAA



A<sub>5</sub>

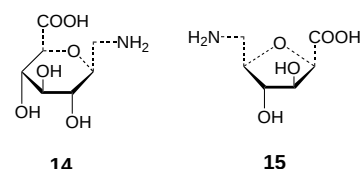
(azasugar acid (ASA))

Scheme 1. Classification of GAAs according to the position of the amino acid moiety on the monosaccharide scaffold. X = O, S, P...;  $n = 0, 1, 2, \dots$ ; Y = CH, CH<sub>2</sub>, S, O, NHCO, CONH, NR;  $u = 0, 1, 2, \dots$ ;  $v = 0, 1, 2, \dots$ ;  $w = 0, 1, 2, \dots$ ; Z = NHAc, OH, H.

substitution of the endocyclic oxygen atom by a nitrogen atom provides azasugar-based A<sub>5</sub> GAAs, referred to herein as azasugar acid (ASA) (Scheme 1). Substitution of the endocyclic oxygen by other heteroatoms (S, P, Se...) can also be envisaged.

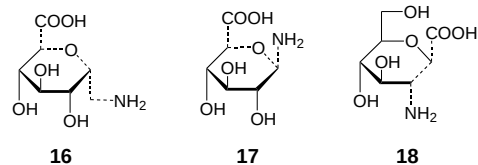
### 3.1. A<sub>0</sub> Sugar Amino Acids

The incorporation of a carboxylic acid and an amino function into a cyclic carbohydrate skeleton results in conformationally restricted SAAs. The rigidity can be used to generate secondary structures, provided that the SAAs are oligomerized or incorporated into short peptides. The SAAs **14**, **15**, and **16** have been studied as dipeptide isosteres (Scheme 2).<sup>[21–24]</sup> Similarly, the SAAs **17** and **18** have been shown to mimic  $\beta$ - and  $\gamma$ -turns when incorporated into short peptide sequences.<sup>[21]</sup> The C3-branched SAA ester **19**<sup>[25]</sup> and the derivatives **20–22**<sup>[26, 27]</sup> have been prepared as building blocks for the synthesis of furanoside-based antisense oligonucleotides. The pyranoside-based oligonucleotide analogues



14

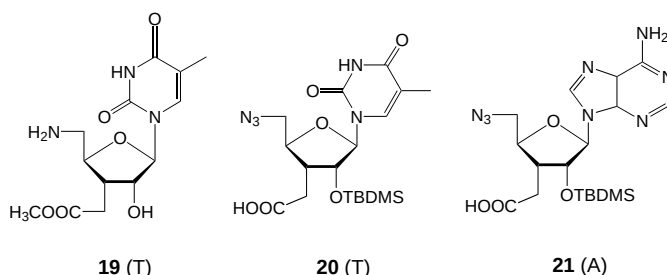
15



16

17

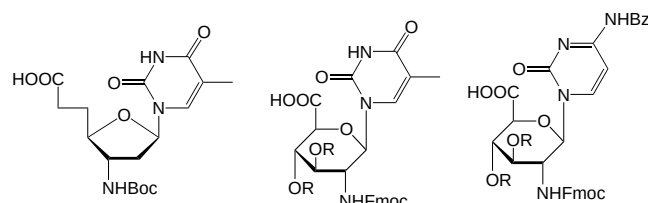
18



19 (T)

20 (T)

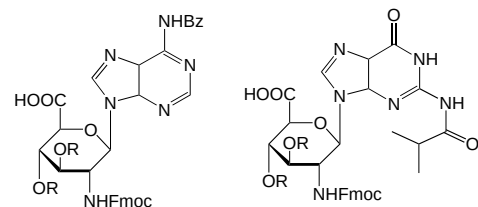
21 (A)



22 (T)

23 (T)

24 (C)



25 (A)

26 (G)

Scheme 2. A<sub>0</sub> GAAs used in the synthesis of peptidomimetics and antisense oligonucleotides (Fmoc = 9-fluorenylmethoxycarbonyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl).

**23–26**<sup>[28]</sup> have been prepared and oligomerized into glucopyranosyl nucleic amides (GNA).<sup>[29]</sup> A list of references for SAAs (A<sub>0</sub>-type) is provided in Table 1.

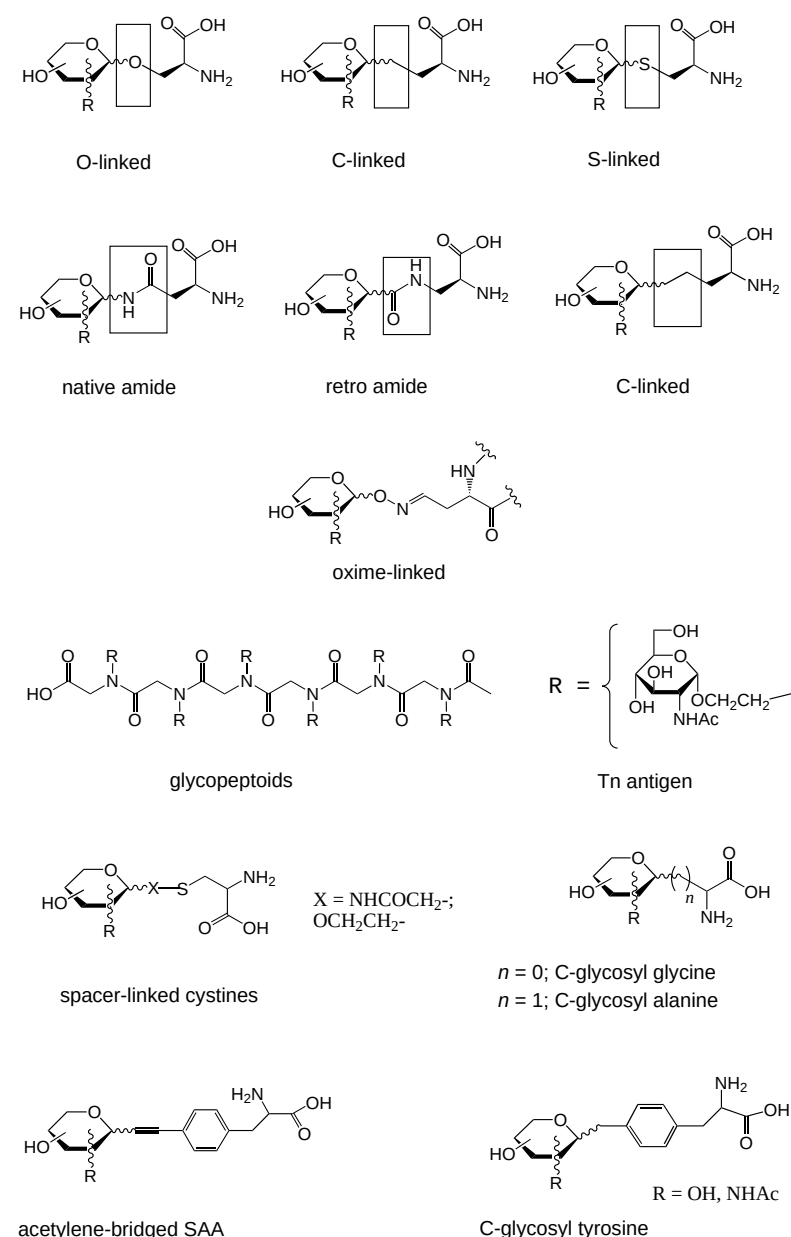
### 3.2. A<sub>1</sub> GAAs

Oligosaccharides attached to polypeptides can modulate protein folding, intra- and intercellular trafficking, receptor binding and signaling,<sup>[30, 31]</sup> enhance the thermal stability of proteins,<sup>[32]</sup> and protect them against proteolytic degradation.<sup>[33, 34]</sup> Carbohydrates attach to proteins through three major types of linkage: a) N-glycoside linkage between the reducing terminal sugar and the amide group of asparagine

(Scheme 3), b) O-glycoside linkage between the sugar and a hydroxy group of an amino acid, most commonly serine and threonine, but also 5-hydroxylysine, 4-hydroxyproline, and tyrosine are known,<sup>[35]</sup> c) ethanolamine phosphate linkage between the C-terminal residue of the protein and an oligosaccharide attached to phosphatidylinositol (GPI anchor). Other naturally occurring linkages include the S-glycoside linkage to cysteine<sup>[4, 5]</sup> and C-glycoside linkage to tryptophan (Scheme 3).<sup>[6, 7]</sup> However, O- and N-linked glycopeptides are metabolically unstable towards glycosidases, an inherent limitation of these materials as potential drugs. Mimics of the naturally occurring glycopeptide linkages have been prepared to overcome these drawbacks.<sup>[36]</sup> For example, the exocyclic oxygen atom in the O-Ser(Thr) linkage has been replaced by a methylene unit<sup>[37–47]</sup> or by sulfur.<sup>[48–52]</sup> N-linked glycopeptides may be mimicked by retro amides,<sup>[53, 54]</sup> glyco-

peptoids,<sup>[55]</sup> and C-linked glycopeptides in which the amide group has been replaced by an ethylene isostere (Scheme 3).<sup>[56–59]</sup> GAAs with an oxime linkage between the sugar and the peptide have been prepared by chemoselective ligation.<sup>[60]</sup> Glycopeptoids (N-substituted oligoglycines)<sup>[55, 61]</sup> and various spacer linked cystines<sup>[62]</sup> are also known. Other potential glycopeptide mimetics are the C-glycosylglycines and C-glycosylalanines (Scheme 3). Both types of SAAs differ from the native O-linked SAA in that the amino acid side chain is shorter by one or two carbon atoms. A short and versatile synthesis of  $\alpha$ -C-glycosylalanines in the fucose, mannose, galactose, and glucose series by means of an asymmetric Strecker synthesis was described recently.<sup>[63]</sup> Acetylene-bridged GAAs<sup>[64]</sup> and C-glycosyltyrosines<sup>[65]</sup> have also been synthesized and incorporated into C-glycopeptides (Scheme 3). The acetylene bridge is less polar than the natural

ether or amide linkage of O- or N-glycopeptides and thus it has been postulated that membrane transport properties are improved. Furthermore, the rigid tether should make the saccharide moieties less flexible, which may result in smaller entropy losses during binding.<sup>[64, 66]</sup> Despite a multitude of synthetic glycopeptide mimetics (Table 1), only a few reports are found in which their bioactivity has been evaluated. For example, an oxime-linked version of the 19 amino acid glycopeptide, drosocin, which has a single site of O-linked glycosylation, was similar to the native molecule in bacteriostatic activity.<sup>[67]</sup> Nevertheless, replacement of the native sugar linkage may result in reduced bioactivity. Studies on model glycoproteins have revealed that the monosaccharide units most proximal to the peptide backbone can profoundly influence local peptide structure.<sup>[68]</sup>



Scheme 3. GAAs for the synthesis of natural and non-natural glycopeptides.

### 3.3. A<sub>2</sub> GAAs

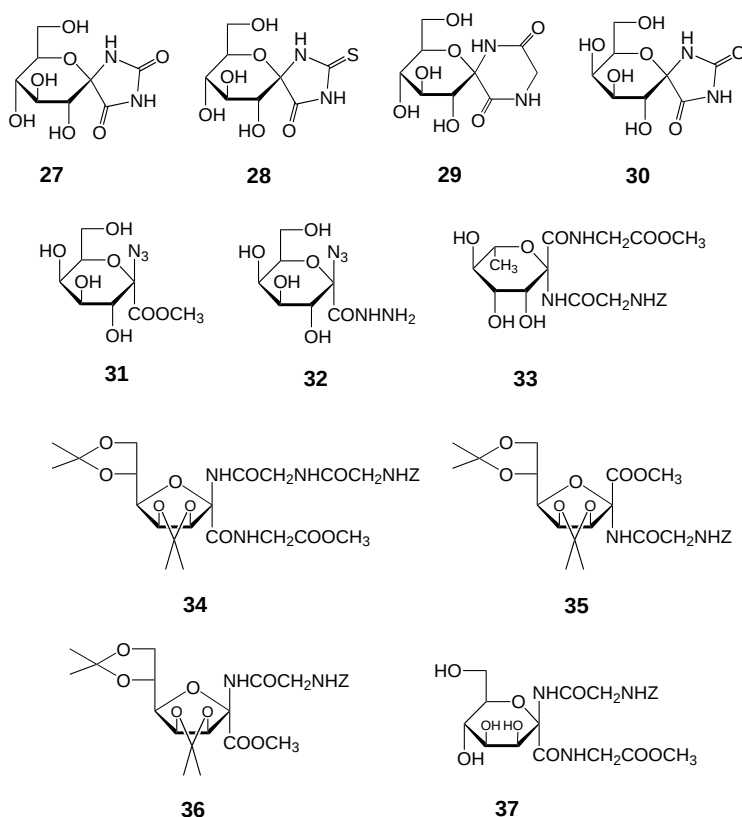
Double substituted A<sub>2</sub> GAAs have been found as components of natural products and as inhibitors of glycogen phosphorylase. For example, the naturally occurring spiroribofuranose hydantoin **10** shows strong herbicidal activity, with no toxicity to microorganisms or animals.<sup>[10]</sup> Stereoisomers and deoxy analogues of **10** (except for the 5-epimer) are not biologically active,<sup>[10, 69–76]</sup> but spirothiohydantoin analogues of **10** maintained herbicidal activity.<sup>[77]</sup> The mode of action of the hydantoin is not completely understood, although a mechanism that accounts for the herbicidal activity has been suggested.<sup>[173]</sup> Other di-substituted spiro-sugar  $\alpha$ -amino acids, such



as **27**,<sup>[78]</sup> **28**,<sup>[79]</sup> and **29**<sup>[80]</sup> are efficient specific inhibitors of muscle and liver glycogen phosphorylase (GP), a major regulatory enzyme of blood sugar levels (Scheme 4). Inhibition of this enzyme can provide a means for controlling blood glucose levels and may lead to new therapeutic agents for the treatment of diabetes.<sup>[81]</sup> Interestingly, compound **29** does not inhibit a wide range of glycosidases, which indicates a specific inhibition of GP.<sup>[80]</sup> In contrast, the galactohydantoin **30** does not inhibit a variety of enzymes, including glycogen phosphorylases, galactosidases, and glucosyl- and galactosyl transferases.<sup>[82]</sup> Similarly, compounds **31** and **32** showed no inhibitory effect against a variety of transferases and galactosidases.<sup>[82]</sup> Several di-, tri-, and tetrapeptides with GAA derivatives of rhamnopyranose **33**,<sup>[83]</sup> mannofuranose **34**–**36**,<sup>[84–86]</sup> and mannopyranose **37**<sup>[84]</sup> have been synthesized (Scheme 4). These compounds may find use as novel N-linked glycoprotein analogues or as  $\alpha,\alpha$ -disubstituted amino acids with the ability to control the secondary structure of short peptides and for the introduction of carbohydrate-recognition sites in synthetic peptides.<sup>[86]</sup> No data on the bioactivity of these short peptides has been reported so far. A list of A<sub>2</sub> GAAs and their derivatives is given in Table 1.

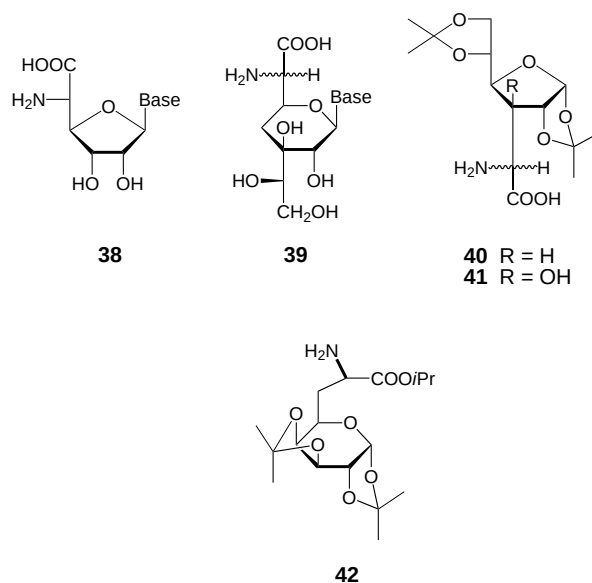
### 3.4. A<sub>3</sub> and A<sub>4</sub> GAAs

Non-anomeric linking of the amino acid moiety to the carbohydrate portion provides A<sub>3</sub> and A<sub>4</sub> GAAs. These



Scheme 4. A<sub>2</sub> GAAs and derivatives with the incorporated anomeric center of a carbohydrate.

GAAs are found in a variety of antibiotics (Scheme 5). The C-glycofuranosyl  $\alpha$ -amino acid **38**<sup>[87–91]</sup> has attracted much attention because of its presence in the polyoxin and

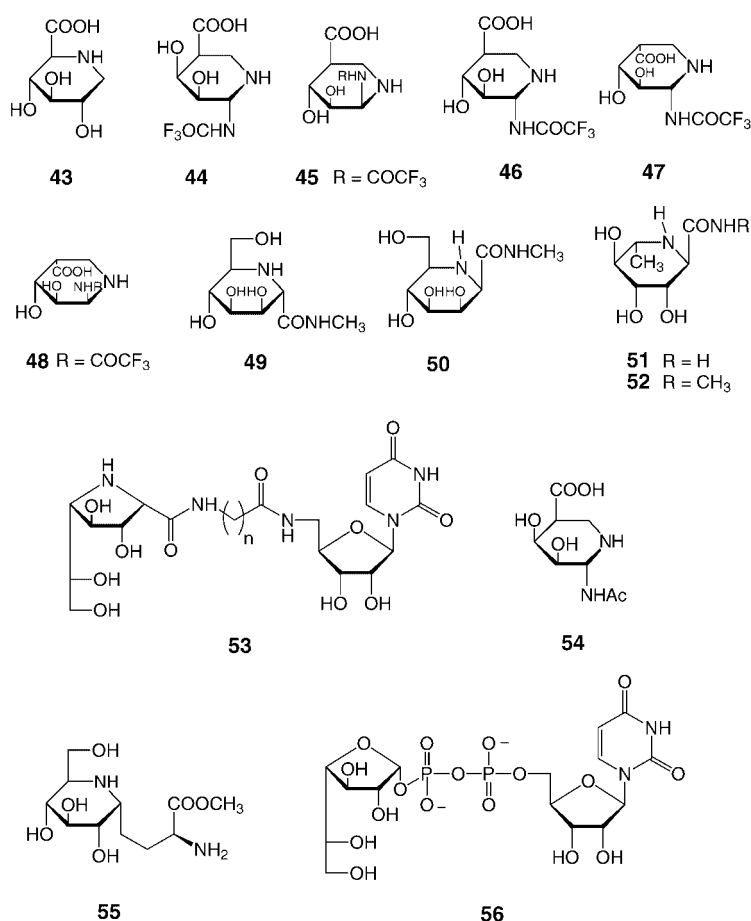


Scheme 5. A<sub>3</sub> GAAs: the amino acid moiety forms the part of a branched carbohydrate structure.

nikkomycin antibiotics, and the C-glycopyranosyl  $\alpha$ -amino acid **39**<sup>[92–94]</sup> is a component of the nucleoside antibiotic ampurimycin. Analogues of the polyoxin-based GAA were synthesized by Rosenthal et al.<sup>[95–97]</sup> For example, compounds **40** and **41** bear the amino acid moiety at C3, instead of at C4 as is the case in polyoxin. Unfortunately, no biological data have been provided for these amino acids. The glycopyranosyl  $\alpha$ -amino acid **42** has recently been prepared and incorporated into a short peptide sequence.<sup>[89]</sup> It has been suggested that the incorporation of these non-natural glycopyranosyl  $\alpha$ -amino acids into native peptides may lead to enhanced resistance against enzymatic degradation and induction of conformational restraint on the peptide.<sup>[89]</sup> Linking the sugar moiety through the amino function of the amino acid provides aminodeoxy sugars with an incorporated amino acid moiety (A<sub>4</sub> GAAs). A list of previously synthesized C-branched sugar amino acids (A<sub>3</sub> and A<sub>4</sub> GAAs) is provided in Tables 1.

### 3.5. Azasugar Acids (A<sub>5</sub> Type)

Replacement of the endocyclic oxygen atom by a nitrogen atom leads to a different class of GAAs, referred to herein as azasugar acids ASAs (Scheme 6). Azasugars have been intensively studied as glycosidase inhibitors, and several potent azasugar-based glycosidase inhibitors have been discovered.<sup>[98]</sup> The ASAs **43**,<sup>[99]</sup> **44**, **45**, and **46** belong to the uronic acid family and are potent inhibitors of



Scheme 6. Azasugar acid (ASA): GAAs in which the endocyclic oxygen atom has been substituted by an amino function.

glucuronidases.<sup>[100]</sup> In contrast the amino acid **47** is a weak glucuronidase inhibitor, and the amine **48** does not inhibit glucuronidase from bovine liver.<sup>[100]</sup> Rather surprising is the behavior of the mannose-based azasugar amides **49** and **50**, which are potent inhibitors of two  $\beta$ -*N*-acetylglucosaminidases (human placenta and bovine liver), but do not show any inhibition of  $\alpha$ -*N*-acetylgalactosaminidase from chicken liver.<sup>[101]</sup> The L-rhamnopyranose-derived amides **51** and **52** are potent inhibitors of naringinase (L-rhamnosidase) and also inhibit the biosynthesis of thymidine diphosphate-L-rhamnose from thymidine diphosphate-D-glucose.<sup>[102]</sup> This may lead to novel carbohydrate-based chemotherapeutic agents for the treatment of mycobacterial infection, since rhamnopyranose occurs in the disaccharide linker between the arabinogalactan polysaccharide and the peptidoglycan regions of the cell wall of *Mycobacterium tuberculosis*. An alternative approach to interfere with the cell wall synthesis of *Mycobacterium tuberculosis* may be the inhibition of *Galf* transferases. In vitro studies have shown that uridine 5'-diphosphogalactofuranose **56** is the donor for the galactosyltransferases involved in the biosynthesis of the cell wall of *Mycobacterium tuberculosis*. The activated glycosyl donor has been mimicked successfully with various glycosyltransferases<sup>[103]</sup> and may provide a new strategy to cope with mycobacterial infections. For example, the ASA conjugate **53**, which contains an amino acid linker between the nucleoside and iminogalactofuranose compo-

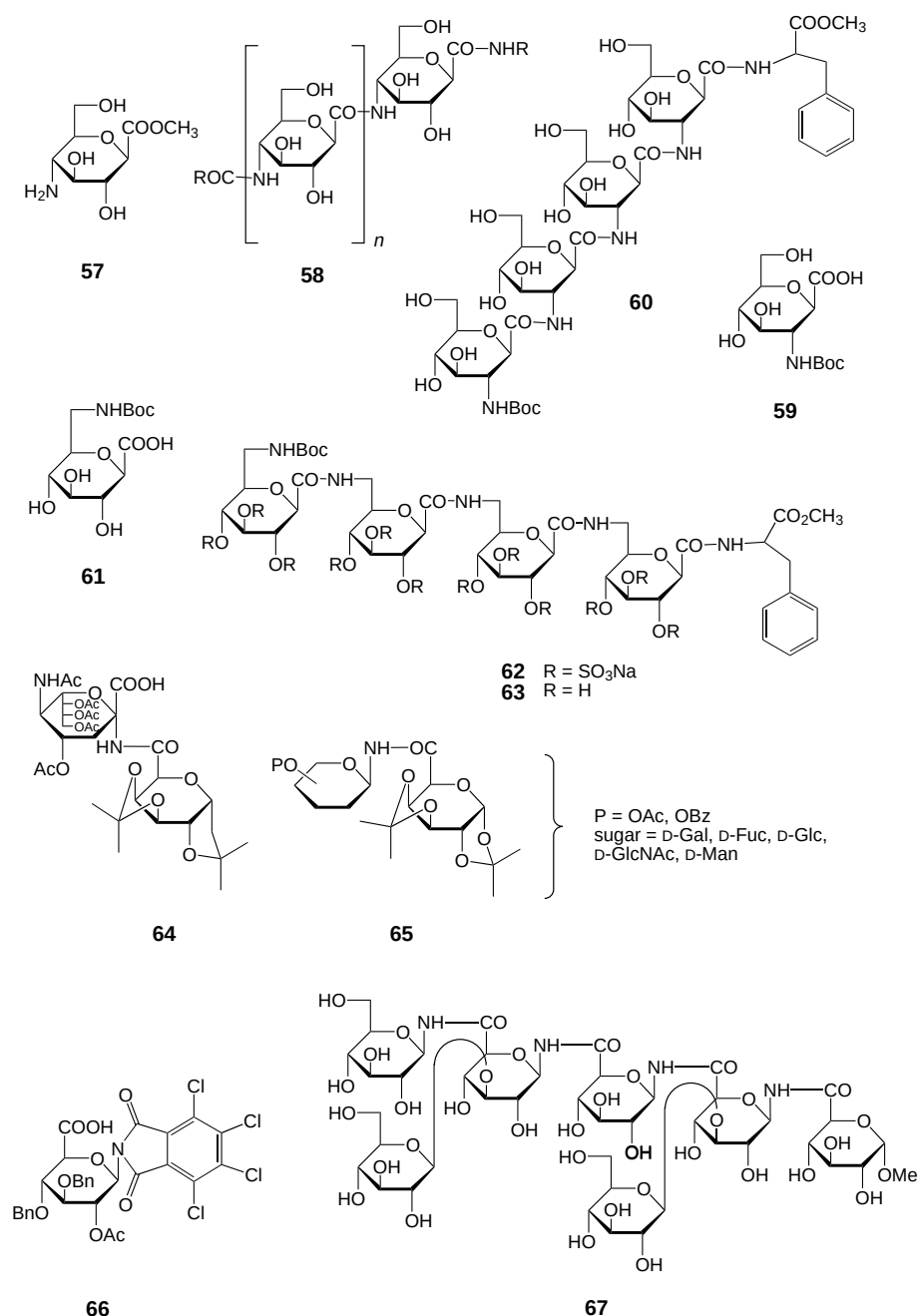
nents, has been suggested as a potential mimic of the natural donor.<sup>[104]</sup> Furthermore, replacement of the labile phosphodiester bonds with amides should increase the stability and cell permeability of these compounds. Another very interesting ASA is the neuraminidase inhibitor siastatin B (**54**),<sup>[105]</sup> which shows inhibitory effects against various neuraminidases,  $\beta$ -glucuronidase, and *N*-acetyl- $\beta$ -D-glucosaminidase. Recently, nojirimycinyl C-(L)-serine (**55**), a combination of a C-GAA and the well-known glucosidase inhibitor nojirimycin, was prepared.<sup>[106]</sup> This compound might be a promising building block to elucidate the biological function of protein glycosylation as a result of its metabolic stability and inhibitory activity against glycosidases. A list of synthetic A<sub>5</sub> GAAs is given in Table 1.

#### 4. Use of GAAs in Combinatorial Synthesis

Monosaccharide building blocks with incorporated amino and carboxylic acid functional groups (GAAs) have been proposed by McDevitt and Lansbury<sup>[1]</sup> as versatile building blocks for combinatorial synthesis. In particular, the well-established chemistry of amide formation is a very attractive strategy to prepare compound libraries of GAA oligomers (glycotides). Synthetic glycotides were proposed as drug candidates because they would not be susceptible to glycosidases and may not be recognized by proteases as a result of the altered backbone relative to the natural substrate.<sup>[1]</sup> Functional group modifications of the polyol moiety could increase the lipophilicity of the molecules and render them more likely to permeate cell membranes.<sup>[1]</sup> Besides their use in peptide coupling reactions, GAAs may also be useful building blocks for other chemical transformations that are compatible with combinatorial strategies, including reductive aminations<sup>[107]</sup> and multicomponent reactions.<sup>[108]</sup>

##### 4.1. Oligosaccharide Mimetics—Homooligomerization of A<sub>0</sub> GAAs

SAAs in which the amino, carboxylic acid, and polyol functions are directly incorporated into a sugar ring have been used as oligosaccharide mimetics (Scheme 7). Lehmann and Fuchs developed polysaccharide analogues in which the glycoside linkages were replaced by amide bonds.<sup>[109]</sup> The amine **57** was exposed to methanolic NaOMe to afford polycondensed amide-linked oligomers **58**.<sup>[110]</sup> The water-soluble condensation products were not further characterized, but could be readily saponified with sodium hydroxide, presumably as a result of the participation of the 7-OH group of the sugar oligomer. Later, Nicolaou et al.<sup>[111]</sup> termed these analogues carbopeptoids because of their hybrid character between carbohydrate and peptide. The difficulties associated with the synthesis of oligosaccharide libraries, for example,

Scheme 7. A<sub>0</sub> GAAs used in the synthesis of oligosaccharide mimetics.

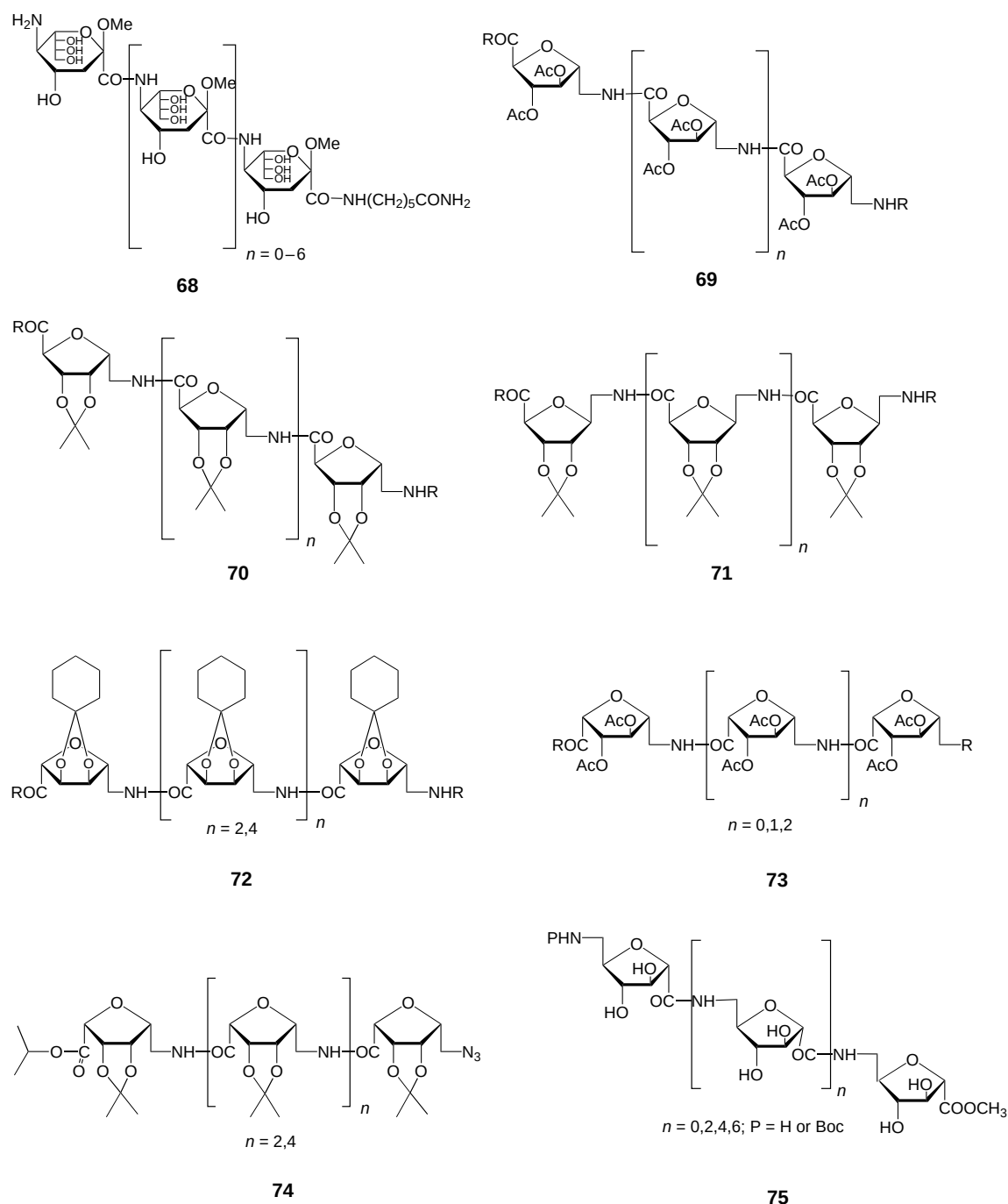
stereocontrol of the newly formed glycoside bond ( $\alpha$  or  $\beta$ ), efficiency of the glycosylation reaction, and the susceptibility towards lysis by glycosidases, were expected to be overcome through the replacement of the glycoside linkage by peptide bonds. The first characterized carbopeptoids were synthesized by Ichikawa et al. by using D-glucosamine-derived SAA building block **59** as a key building block. Elongation of **59** afforded the tetramer **60**, which after O-sulfation showed a strong inhibitory potency against HIV infection of CD4 cells.<sup>[113]</sup> Similarly, oligomerization of the Boc-protected SAA **61** followed by sulfation and deprotection gave the  $\beta(1 \rightarrow 6)$ -linked carbopeptoid **62**, which strongly inhibited the HIV infection of MT2 cells.<sup>[112]</sup> Interestingly, the nonsulfated analogue **63** did not show any measurable inhibitory effect

in the same assay. Sabesan<sup>[114]</sup> prepared several amide-linked sugar dimers **64** and **65** in which the nitrogen atom of the peptide bond is connected to the anomeric carbon atom (Scheme 7). He suggested that this type of amide linkage might be sterically more compatible with that of a glycoside oxygen atom, but no biological data were provided. Similarly, the sugar amino acid **66** was used in the synthesis of the carbopeptoid **67**, an analogue of the naturally occurring phytoalexin elicitor (Scheme 7). Unfortunately, the heptamer **67** was not biologically active.<sup>[115]</sup>

Analogously to amino acids, sugar–amino acid hybrids induce secondary structures by oligomerization (Scheme 8).<sup>[116–124]</sup> Gervay and co-workers synthesized dimeric to octameric (1  $\rightarrow$  5)-linked sialo-oligomers **68** in solution<sup>[118]</sup> and in the solid phase.<sup>[119]</sup> Circular dichroism (CD) and NH/ND exchange rates were used to show that oligomers of constrained carbohydrate-derived amino acids form stable secondary structures in water. Fleet and co-workers investigated the ability of several 5-aminomethyltetrahydrofuran-2-carboxylate oligomers to form secondary structures (Scheme 8).<sup>[116, 117, 120–125]</sup> The tetrameric *trans* SAAs **69** and **70** did not form strong intramolecular hydrogen bonds in chloroform, whereas octameric **70** showed a strong intramolecular hydrogen bonding pattern reminiscent of a left-handed  $\alpha$ -helix.<sup>[120]</sup> The tetrameric *cis* SAAs **71**–**73** form secondary structures in solution (CDCl<sub>3</sub>) similar to a repeating  $\beta$ -turn. Tetramer **72**, which has

the opposite configuration of **71** and an isopropylidene rather than a cyclohexylidene protecting group, had a very similar <sup>1</sup>H NMR spectrum, which indicates that the different ketal protecting group has very little effect on the conformation in solution.<sup>[120, 124]</sup> Recently, the synthesis of tetrameric **72** was extended to the octamer; the structure of this compound in a solution of chloroform was again suggested to be a repeating  $\beta$ -turn.<sup>[124]</sup> Interestingly, the unprotected tetramer **72** dissolved in methanol exhibited similar secondary structures to those of protected tetramer **72** in chloroform.<sup>[124]</sup> The known oligomers **74**<sup>[123]</sup> and **75**<sup>[126]</sup> do not form well-defined secondary structures.

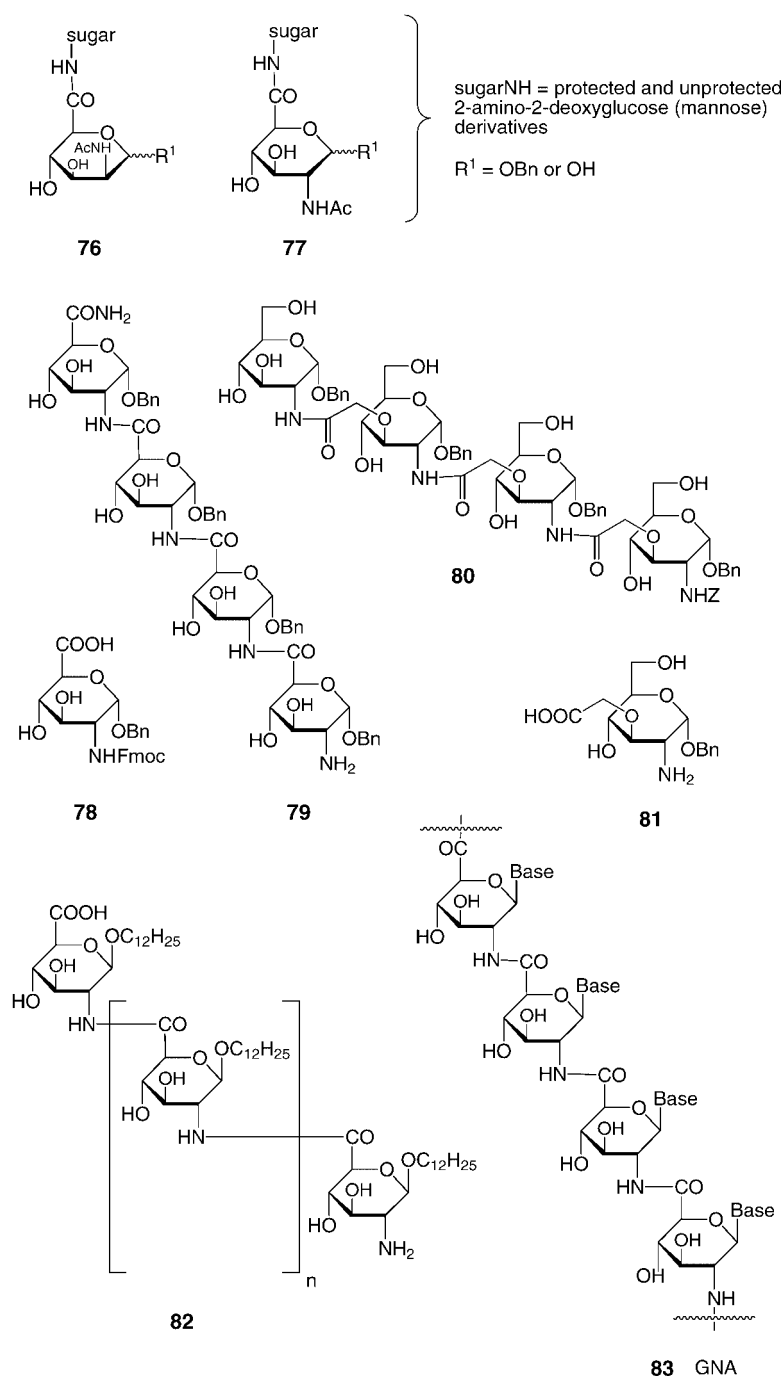
SAA oligomers in which the anomeric carbon atom is not part of the linkage region have also been prepared



Scheme 8. Homooligomerization of  $A_0$  GAAs. Some oligomers induce secondary structures in organic solvents.

(Scheme 9). Yoshimura et al reported the first synthesis of (2→6) amido-linked disaccharides **76** and **77** by using 2-acetamido-2-deoxy-D-glucuronic and 2-acetamido-2-deoxy-D-manuronic acid, respectively.<sup>[127]</sup> Wessel and co-workers subsequently oligomerized the Fmoc-protected 2-amino-2-deoxy-D-glucuronic acid **78** to the tetramer **79** in the solid phase.<sup>[128]</sup> The same group also synthesized the tetramer **80**, which has normuramic acid (**81**) as a building block.<sup>[129]</sup> The polymerization of 1-O-dodecyl-2-amino-2-deoxy-β-D-glucopyranosiduronic acid afforded polymeric SAA **82**, which forms closely packed monolayers upon spreading of a dilute DMSO/CHCl<sub>3</sub> solution on a pure water surface.<sup>[130]</sup>

SAAs have also been used to prepare compounds with potential antisense properties. The replacement of the phosphodiester backbone in DNA and RNA by an achiral peptide bond has been actively pursued. In particular, the low membrane permeability (negative charge density) and the high susceptibility to nucleolytic cleavage of the phosphodiester backbones might be improved with neutral amide linkages. Recently, ribose-derived SAA nucleotides have appeared and have been used as monomers for oligomerization. Fujii and co-workers prepared the 2-deoxyribose building block **22(T)** (Scheme 2), which underwent solid-phase oligomerization to the 10-mer level.<sup>[174]</sup> Robbins et al. synthesized the nucleo-



Scheme 9. Amide-linked A<sub>0</sub> GAA oligomers in which the anomeric (pseudo-anomeric) center is not involved in the linkage (Z = benzyloxycarbonyl, Bn = benzyl).

sides **19**(T), **20**(T), and **21**(A) and investigated their oligomerization.<sup>[131, 132]</sup> Pyranoside-based SAAs were investigated as potential building blocks for new antisense agents by Goodnow et al.<sup>[28]</sup> The four glucosamine-based oligonucleotide analogues **23**(T), **24**(C), **25**(A), and **26**(G) (Scheme 2) were synthesized<sup>[28]</sup> and incorporated into glucopyranosyl nucleic amides (GNA) **83**<sup>[29]</sup> (Scheme 9) to afford the homopyrimidine sequence (H–TCTTCCTCTCTCT–Lys–NH<sub>2</sub>) and a decameric oligomer (H–TCACTAGATG–Lys–NH<sub>2</sub>). The binding affinities and selectivities of these oligomers to DNA and RNA targets were determined by measuring duplex

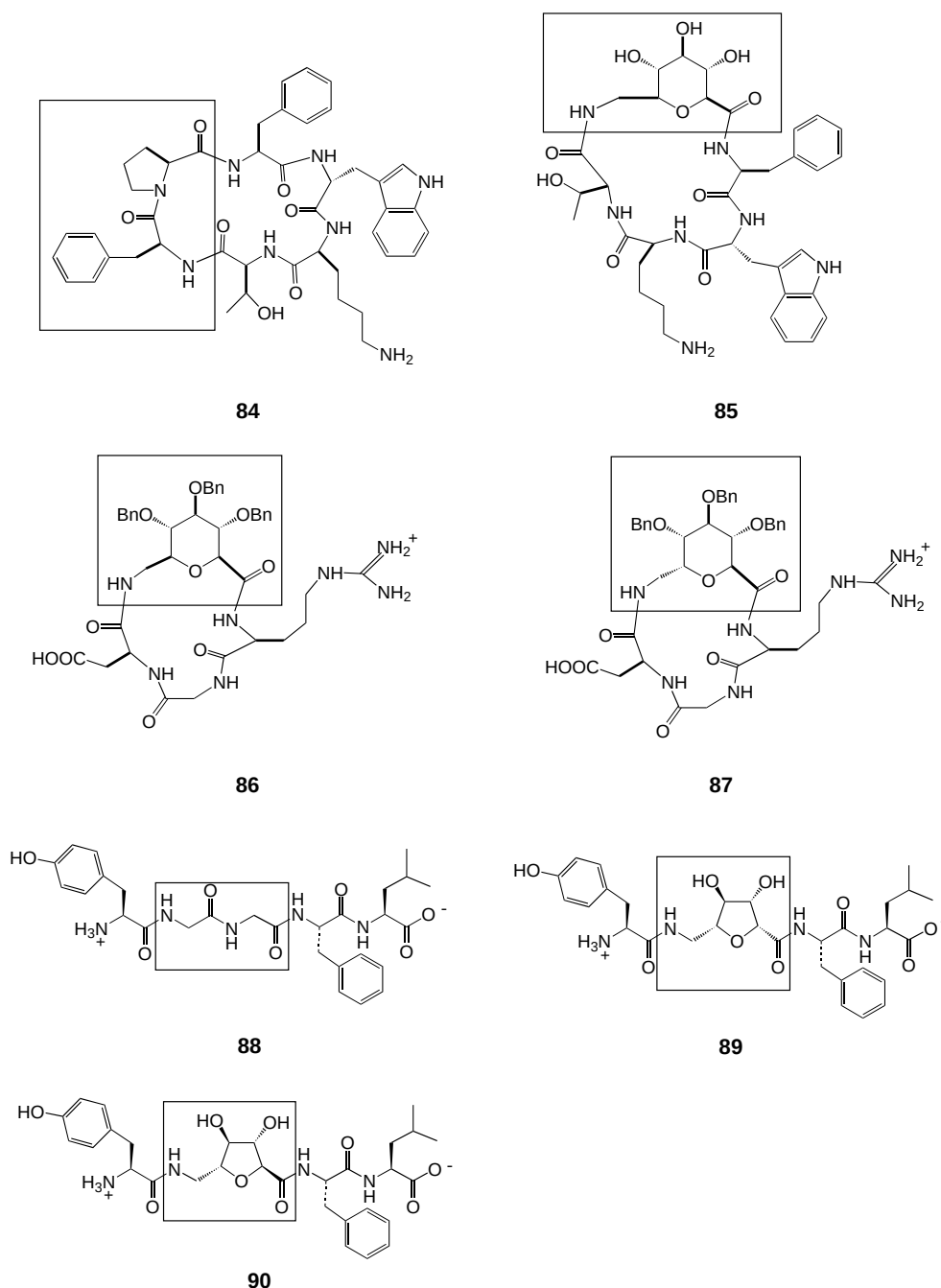
formation and melting temperatures. The results demonstrated that GNAs are able to mimic some binding properties of DNA and RNA. In all cases the calculated changes in entropy for GNA/DNA and GNA/RNA melting transitions, compared to those for the corresponding DNA/DNA and DNA/RNA were consistent with the idea that GNA oligomer conformation is already organized and requires little reorganization.

## 4.2. Oligomerization of SAAs with Other Amino Acids

The condensation of SAAs with amino acids provided conjugates, which were termed peptido-saccharides, saccharide-peptide hybrids, peptide-sugar hybrids, and saccharopeptides, and have important structural and biological features. One of the thrusts in this field is the use of SAA–amino acid conjugates as peptidomimetics. Kessler and co-workers were the first to demonstrate the potential of SAA as peptidomimetics.<sup>[21, 22]</sup> For example, the Pro–Phe dipeptide sequence in the somatostatin analogue cyclo-(Pro–Phe–D-Trp–Lys–Thr–Phe) **84** was replaced by the dipeptide isostere **14** (Scheme 2) to give the potent hexapeptide mimetic **85** (Scheme 10).<sup>[21]</sup> Furthermore, they incorporated the SAAs **14** and **16** into cyclic peptides that contained the RGD (Arg–Gly–Asp) motif. The cyclic pentapeptide cyclo-(–Arg–Gly–Asp–D-Phe–Val–) binds selectively to the  $\alpha_v\beta_3$  receptor of the integrin family. Replacement of the two amino acids D-Phe–Val by the dipeptide isosteres **14** and **16** afforded the potent peptidomimetics **86** and **87** with high  $\alpha_v\beta_3$  activity (IC<sub>50</sub> = 25 nM for **86**) and 150 nM for **87**). Interestingly, the peptidomimetic **86**, which contains the flexible *cis* SAA, also exhibited a high affinity for the  $\alpha_{IIb}\beta_3$  receptor (IC<sub>50</sub> = 13.4 nM), which is absent in SAA-modified peptide **87** incorporating the *trans* SAA **16**.<sup>[24]</sup> This route opens the door to the development of novel receptor- and receptor-subtype-selective agents based on sugar platforms.<sup>[133–135]</sup> Chakraborty et al. incorporated the furanoid SAA **15** (Scheme 2) into Leu–enkephalin sequence **88**.<sup>[23]</sup> Replacement of the Gly–Gly sequence in the Leu–enkephalins by the isostere SAA **15**

afforded the biologically active peptide **89**, which has an activity similar to that of Leu–enkephalin **88** (Scheme 10). Conformation analysis by means of CD, temperature coefficients of amide proton chemical shifts, and molecular dynamics revealed the presence of a nine-membered  $\beta$ -turnlike structure, absent in the saccharopeptide **90**, which contains a *trans* SAA.

The dimer **91** generated from sialic acid and glycine proved to be a moderate inhibitor of *Clostridial* sialidase (Scheme 11).<sup>[136]</sup> Conjugate **92**, which consists of an alternating sequence of SAA and  $\beta$ -amino acid residues (D- and L-



Scheme 10.  $A_0$  GAA-based dipeptide isosteres which have been incorporated into short peptide sequences. The peptidomimetics **85**, **86**, **87**, and **89** are biologically active.

aspartic acid) was prepared by Ichikawa and co-workers. These hybrids are potent inhibitors of lung tumor cell invasion.<sup>[137]</sup> Incorporation of SAAs into the C-terminus of Leu- and Met-enkephalins produced selective and potent  $\delta$ -opioid receptor agonists.<sup>[138]</sup> For example, pharmacological evaluation showed that glycopeptide **93**, which contains the Leu-enkephalinamide sequence, was 40 times more potent than Leu-enkephalinamide itself.<sup>[138]</sup> Recently, Kessler and co-workers demonstrated that the derivatization of the amino acid side chain in biologically active peptide compounds with SAAs influences activity and selectivity.<sup>[24]</sup> For example, peptide **94**, which is modified with a lysine side chain, showed

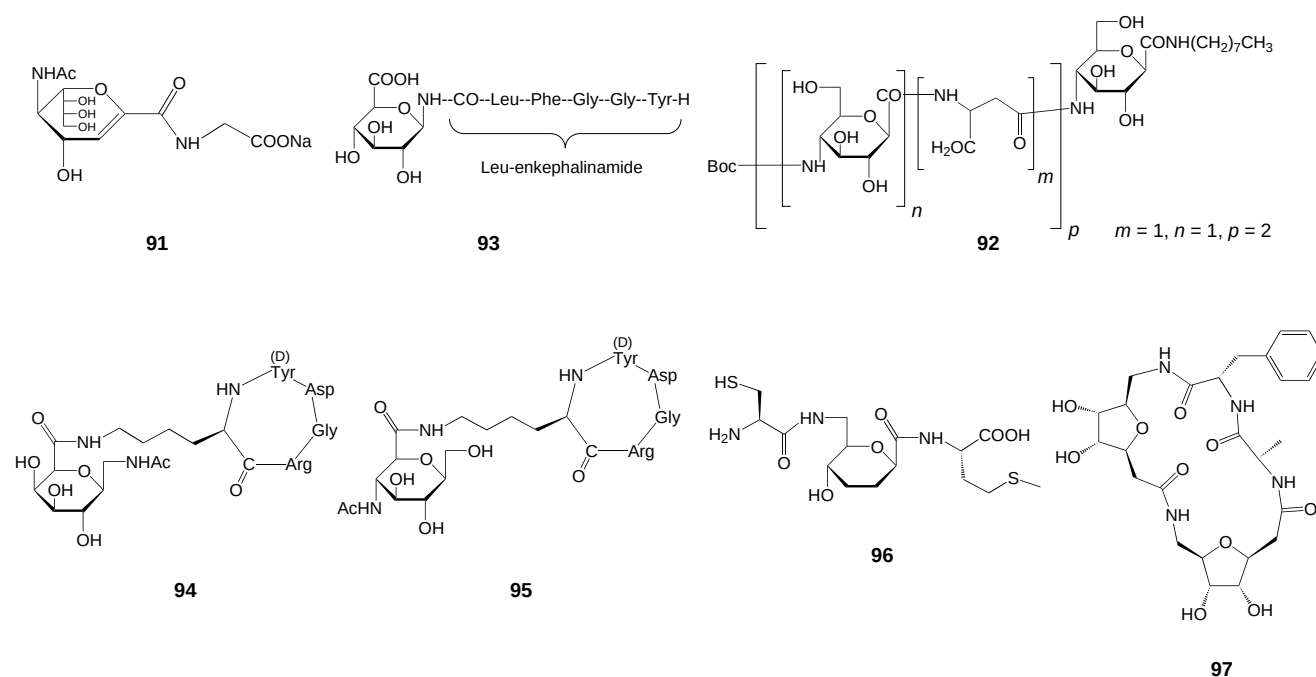
the highest activity for the  $\alpha_v\beta_3$  receptor ( $IC_{50} = 24.7$  nM) in a series of RGD peptides.<sup>[24]</sup> Likewise, RGD peptide **95**, which is derivatized with a side chain, had a lower uptake in the liver than that of the nonglycosylated peptide. As a result, the initial blood concentrations were doubled.<sup>[24]</sup> SAA-based protein farnesyl transferase (PFT) inhibitors have also been reported.<sup>[139]</sup> For example, the saccharopeptide **96**, which contains a dipeptide isosteric sugar amino acid, inhibits bovine PFT ( $IC_{50} = 214$   $\mu$ M).

Recently, cyclic hybrids between sugar amino acids and amino acids were proposed as potential artificial receptors.<sup>[140]</sup> Van Boom and co-workers prepared several tetrameric hybrids in the solid phase and investigated their ability to form secondary structures. Hybrid **97** adopts a preferred conformation in water (Scheme 11). The coupling constant of the amide proton of alanine to its neighboring  $\alpha$  proton is of the same order of magnitude as the coupling constants  $J_{Na}$  of a linear peptide that has an  $\alpha$ -helical structure. It is anticipated that combinatorial exploitation of this solid-phase protocol may eventually lead to artificial receptor libraries based on sugar amino acid building blocks.

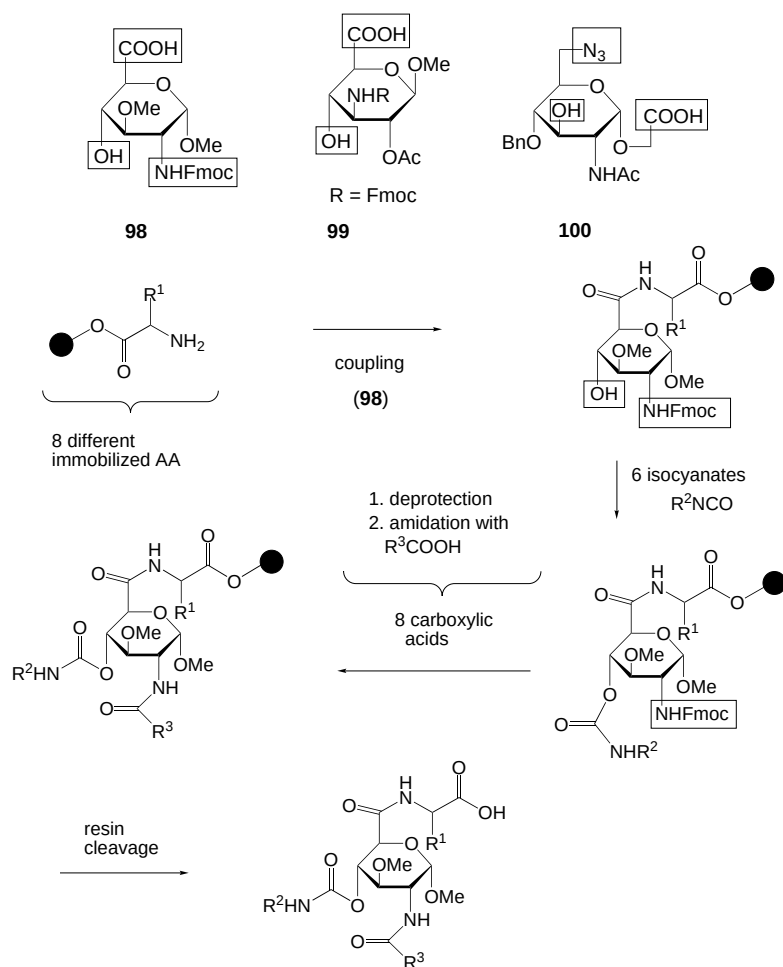
### 4.3. SAAs as Building Blocks for Sugar-Platform Libraries

Carbohydrates have the potential to be used as highly functionalized rigid scaffolds.<sup>[133–135, 141–144]</sup>

In particular, the use of sugar-derived skeletons as non-peptidomimetics of somatostatin (a cyclic tetradecapeptide)<sup>[134]</sup> demonstrated for the first time that sugars might be privileged platforms. Sofia et al.<sup>[145]</sup> elaborated on this idea and reported the synthesis of encoded trifunctionalized saccharide scaffolds termed “universal pharmacophore-mapping libraries”. Two sugar building blocks **98** and **99**, which have a three-point attachment motif that consists of a carboxylic acid moiety, a free hydroxy group, and a protected amino group, were used for the construction of the library (Scheme 12). The free carboxylic acid was first treated with eight amino acids supported on trityl TentaGel resin, followed

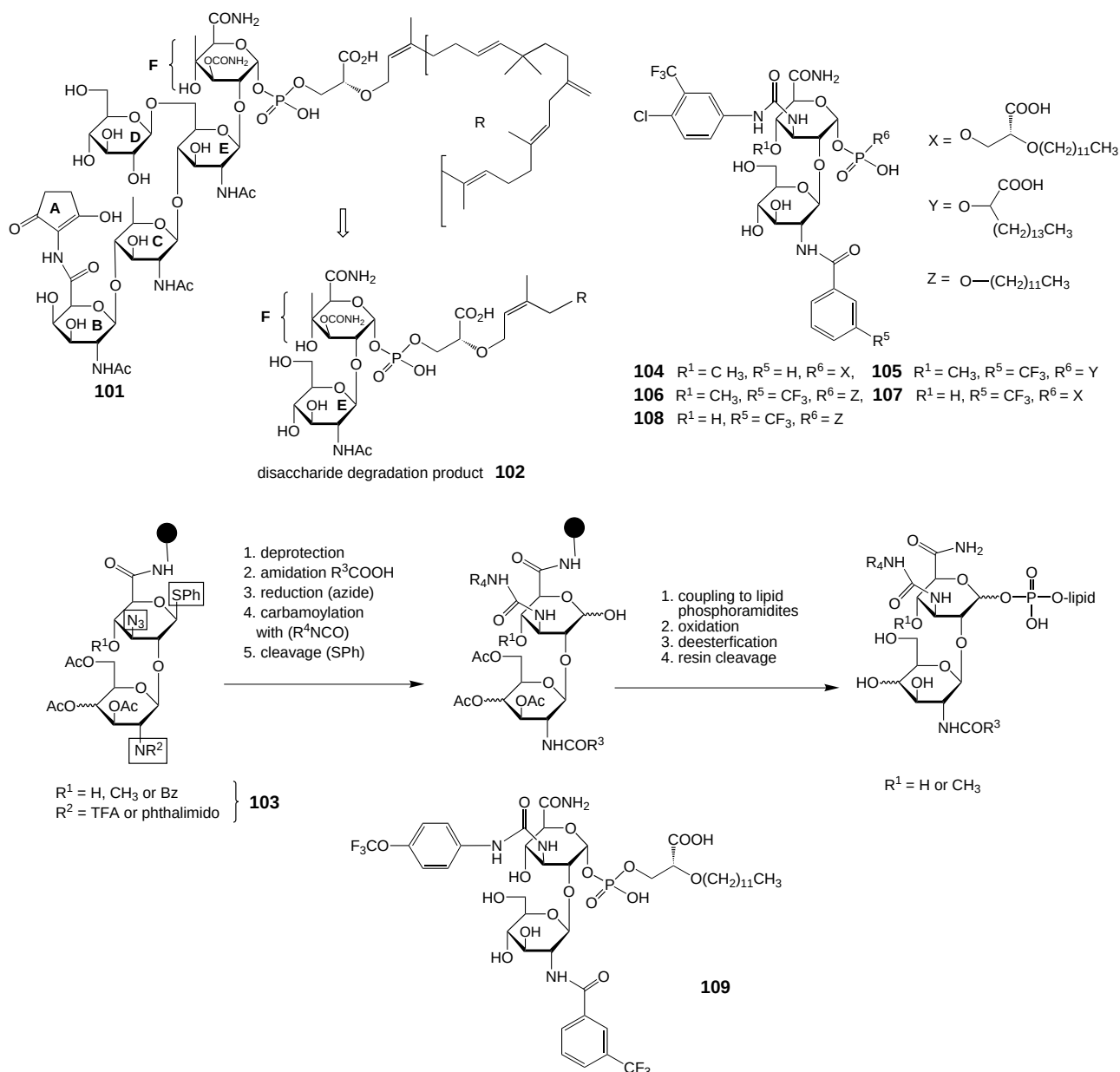


Scheme 11. GAAs linked to amino acids or peptides. Linking GAAs to oligopeptides influences the pharmacokinetic properties of biological active peptides (**93–95**). This approach can also be used to produce agents with anticancer- (**92**) and inhibitory potential (**96**), and may also find application in the synthesis of synthetic receptors (**97**).



Scheme 12. Synthesis of “universal pharmacophore libraries” based on a three-point attachment motif.<sup>[145, 146]</sup>

by carbamate formation at the free hydroxy site by using six isocyanates. Finally, the deprotected amino functional group was acylated with eight different carboxylic acids. Deacetylation (when necessary) and cleavage from the resin gave  $16 \times 48$  sub-libraries. Recently, a 12000-compound library was prepared by using **100** as a building block.<sup>[146]</sup> Sofia et al. also prepared a disaccharide library which mimics the transglycosylase inhibitor moenomycin A (Scheme 13).<sup>[147]</sup> Moenomycin A (**101**) is a pentasaccharide that contains a long lipid chain, which is attached to the reducing sugar F through a phosphoglycerate unit. Degradation studies, in conjunction with limited directed analogue synthesis, revealed that cell wall inhibitory activity was retained in disaccharide core structure **102**. Sofia et al. chose the supported disaccharide **103**, which is substituted with two protected amino functions and a thiophenylglycoside donor, to explore modifications at C1, C3, and C2' (Scheme 12). Analogues in which the GlcNAc moiety was substituted by a GalNAc moiety were also investigated. Initially, the trifluoroacetate- or phthalimido-protected amino function at C2' was deprotected and converted into the amide with a variety of activated carboxylic esters. After reduction of the azide and carbamylation or amidation (not shown), the acetal groups were cleaved. The product

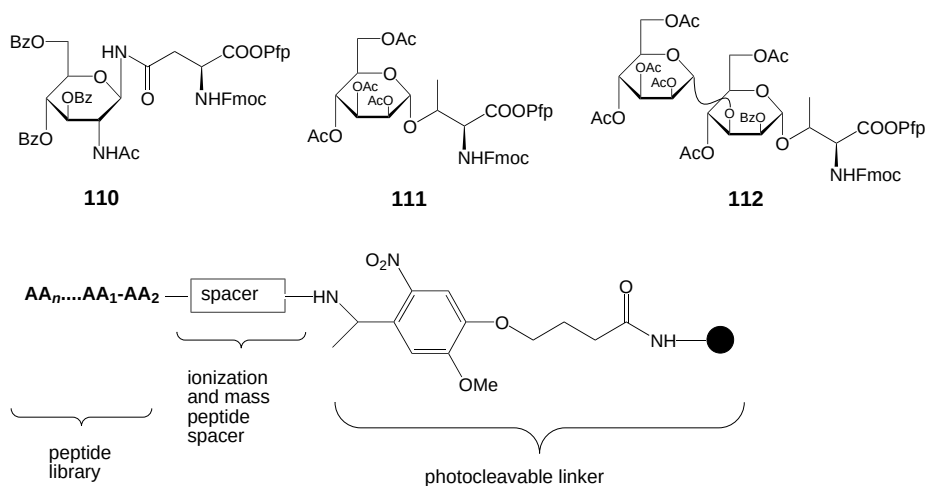
Scheme 13. Synthesis of a library of antibacterial disaccharides that mimic moenomycin A.<sup>[147]</sup>

was coupled to a variety of phosphoramidites, followed by oxidation, to give the desired phosphate intermediate. Finally, deprotection and cleavage from the resin afforded a 1300-membered disaccharide library, which was screened for both inhibition of bacterial cell wall biosynthesis and inhibition of bacterial growth. The results indicated that the replacement of the moenomycin glycerate lipid unit with either a 2-hydroxypropionic acid unit or a simple straight chain C12 lipid leads to compounds whose antibacterial activity is retained. In addition, all active disaccharides contained a substituted aromatic urea at C3. Interestingly, compounds **104–109** were effective against a strain of *E. faecium* that is naturally resistant to moenomycin. Furthermore, disaccharides **104–109** were shown to be as potent as the clinically used vancomycin as inhibitors of cell wall biosynthesis.

#### 4.4. Libraries from GAA derivatives of O- and N-linked Glycopeptides

Simple O-GAAs with protected<sup>[148–152]</sup> and unprotected sugar residues<sup>[153]</sup> as well as N-linked amino acids<sup>[148–152]</sup> have been used as building blocks to generate glycopeptides that can mimic oligosaccharide structures.<sup>[148–152]</sup> An impressive example is the synthesis of a 300 000-membered ladder-encoded<sup>[154]</sup> glycopeptide library by Meldal and co-workers.<sup>[149]</sup> The Pfp-activated (Pfp = pentafluorophenyl) glycosyl amino esters **110**, **111**, and **112** and a variety of activated amino esters were used to generate a heptaglycopeptide library in the solid phase by using a photocleavable linker (Scheme 14). Each GAA was labeled with carboxylic acid tags to allow unambiguous identification of the glycan moiety. The glycopeptide sequence on the bead was decoded by photolytic





Scheme 14. GAA building blocks used in the synthesis of a 300 000-membered glycopeptide library (Pfp = pentafluorophenyl).<sup>[149]</sup>

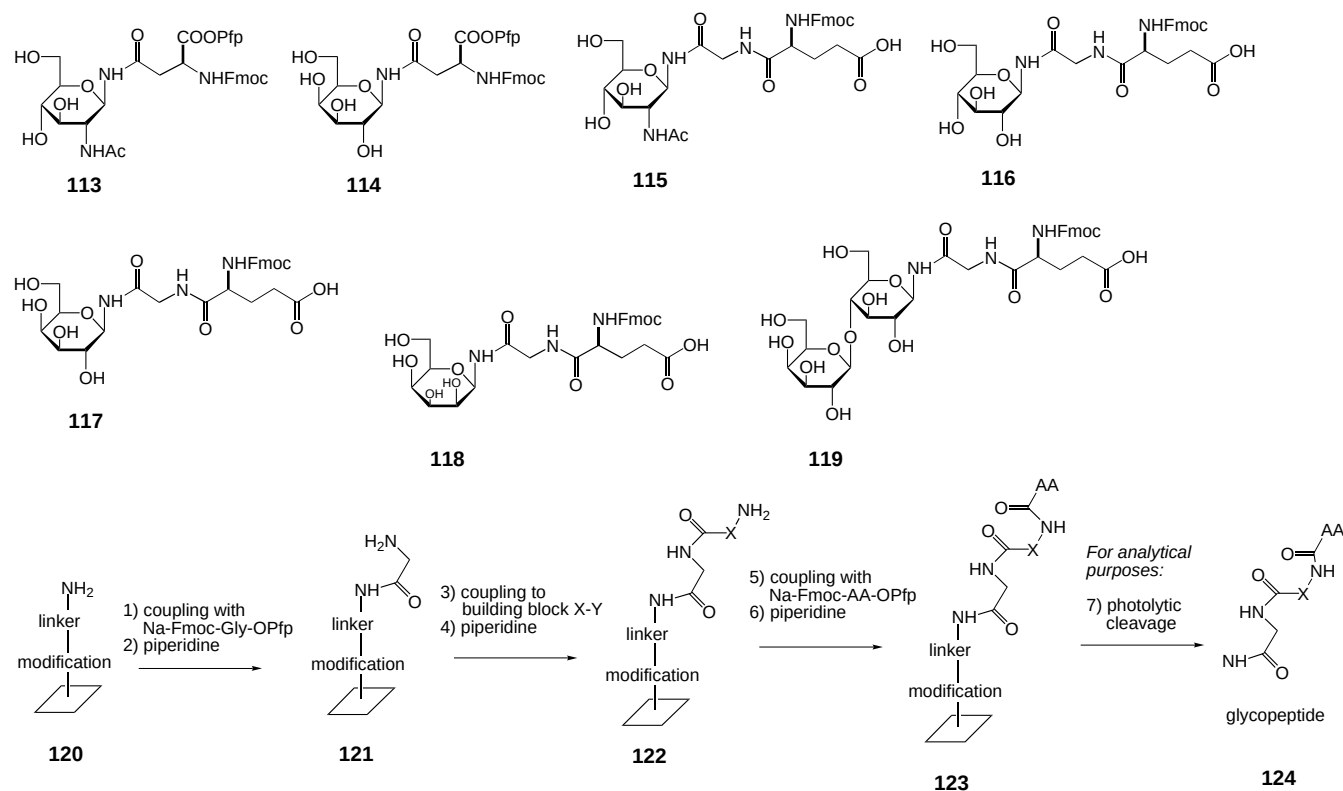
release and subsequent analysis of the resulting mass ladder of glycopeptide fragments by MALDI-TOF mass spectrometry. The synthesized library was screened “on bead” against the fluorescence-labeled lectin from *Lathyrus odoratus*, which shows a weak specificity for the  $\alpha$ -methylglycosides of mannose, *N*-acetylglucosamine, and glucose. Interestingly, the most active compounds were glycopeptides that contain only one mannose residue.

Hummel and co-workers used the sugar-unprotected N-glycopeptide building blocks **113**–**119** for the synthesis of a glycopeptide library on a continuous surface (SPOT syn-

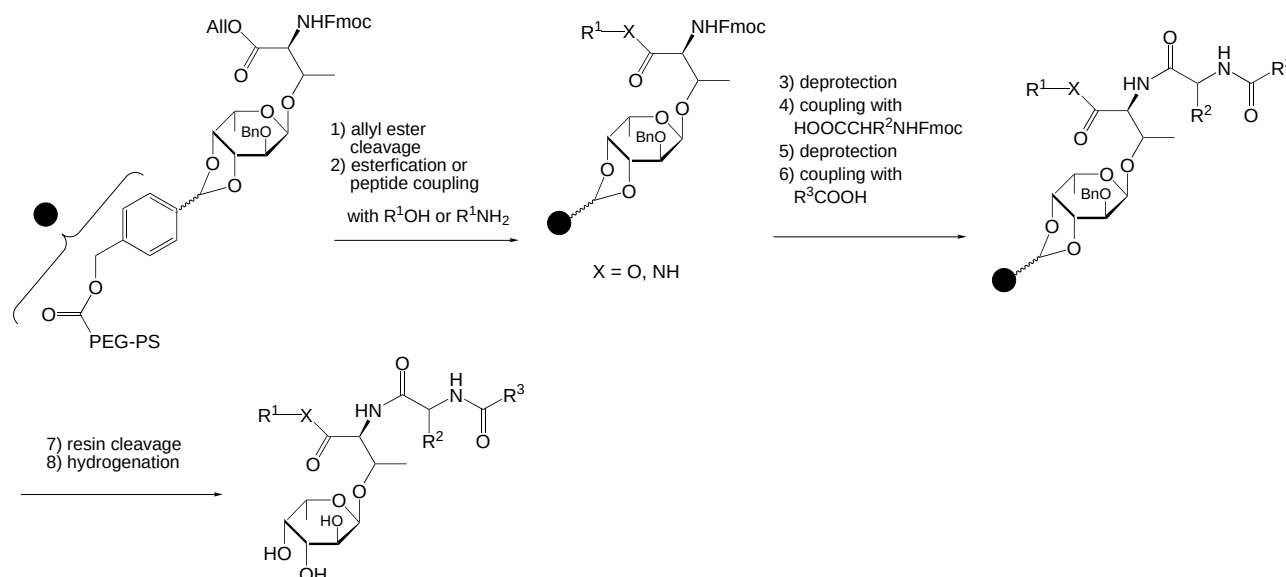
thesis). SPOT synthesis on cellulose is a highly effective method for the rapid preparation of spatially addressable peptides (Scheme 15).<sup>[153]</sup> Initially, the cellulose membranes were modified by treatment with epibromohydrin and 4,7,10-tridecanediamine to provide homogeneous amino functionalization. For analytical purposes a Fmoc-protected photocleavable linker was coupled with the amine to provide, after reaction with piperidine, the immobilized amine **120**. Subsequently, the first amino acid *N*<sup>α</sup>-Fmoc-Gly-OPfp was coupled to the continuous surface. The remaining free amino functions were capped with a solution of acetic anhydride in methanol. In the second coupling step, the seven GAA building blocks **113**–**119** were coupled to the

supported glycine, followed by deprotection. The coupling cycle was repeated with another amino acid. Highly pure tripeptides were obtained upon cleavage from the resin by means of UV irradiation (Scheme 15).

A library that consists of sialyl Lewis<sup>x</sup> mimetics was reported by Wong and co-workers (Scheme 16).<sup>[152]</sup> Fucose, which contains the three hydroxy groups required for the recognition of sialyl Lewis<sup>x</sup> by E-selectin, was retained as the only carbohydrate moiety, while the other three sugar residues were replaced with L-threonine and its derivatives. A fucosylated threonine amino acid residue was immobilized



Scheme 15. SPOT synthesis of an O- and N-linked glycopeptide library.<sup>[153]</sup>



Scheme 16. Synthesis of a library of sialyl Lewis<sup>X</sup> mimetics (PEG = polyethyleneglycol, PS = polystyrene).<sup>[152]</sup>

on a carboxy-functionalized resin through an acid-sensitive *cis* 1,2-diol protecting and anchoring group. The allyl group was first cleaved, and the acid function was then derivatized as an ester or amide, followed by a conventional peptide coupling cycle and capping (Scheme 16). The deprotected and purified compounds were tested against E- and P-selectins and showed only moderate binding affinities.

#### 4.5. Library Synthesis by Using GAAs Not Derived from O- and N-linked Glycopeptides

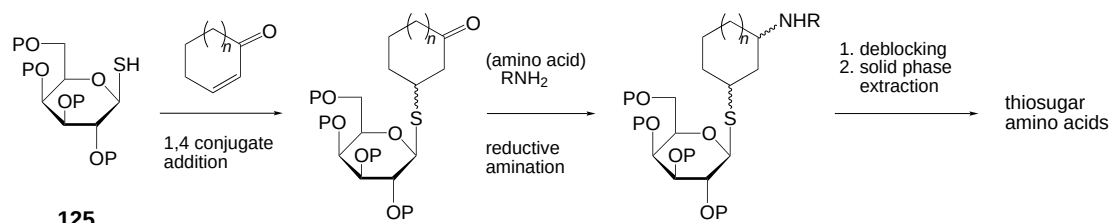
Among the mimics of the naturally occurring glycopeptides, the S-GAA family has attracted considerable interest over the years. The driving force behind the synthesis of S-glycosides has been the production of glycomimetics with enhanced stability toward chemical and enzymatic degradation. Furthermore, the synthesis of S-glycosides is less complicated than the synthesis of C-glycosides. The first combinatorial approach towards S-GAA libraries (carbohydrids) was reported by Hindsgaul and co-workers (Scheme 17).<sup>[107]</sup> Hydrophobically tagged 1-thiogalactose derivative **125** underwent Michael reactions with five different Michael acceptors to yield diastereomeric adducts. In the second step, the ketone groups in the Michael adducts were reductively aminated with six different carboxy-protected amino acids. After deprotection, thirty (5 × 6) thiosugar amino acids were obtained as mixtures of four diastereomers each. The highlight of this

approach is the use of fatty acid carbohydrate esters as hydrophobic tags, which permit the quantitative adsorption of the reaction products derived from the starting sugar onto reversed-phase C-18 resin. The excess organic reagents and by-products could be removed completely by washing with methanol, whereas the final purified product was eluted with hexane. One of the compounds of this library was found to be a competitive inhibitor of  $\beta$ -galactosidase from *E. coli*, with an inhibition constant of 1.7  $\mu$ M. Since then, supported thiolates have been used in the solid-phase preparation of glycomimetics.<sup>[52, 155]</sup>

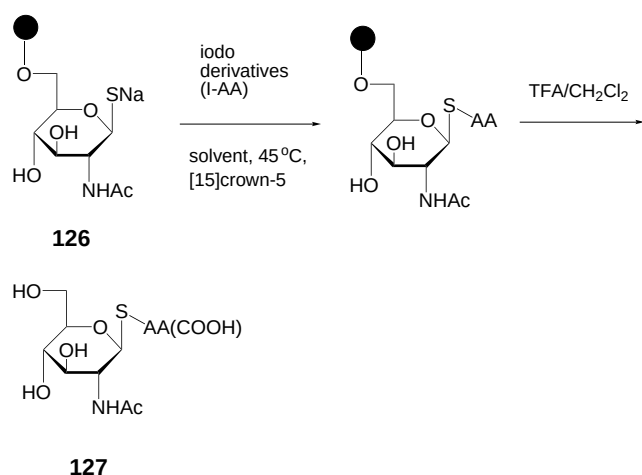
Hummel and Jobron described the synthesis of several unprotected S-GAA building blocks in the solid phase (Scheme 18).<sup>[52]</sup> The key step in their synthesis is the reaction of a supported sodium thiolate **126** with iodo derivatives of amino acids (I-AA) in the presence of [15]crown-5 as complexing agent. Resin cleavage with concomitant acid deprotection afforded various S-GAAs **127**, which can be used as building blocks in the combinatorial synthesis and solid-phase synthesis of S-glycopeptides.

#### 4.6. Combinatorial Approaches Towards Glycopeptides Derived from A<sub>2</sub> GAAs

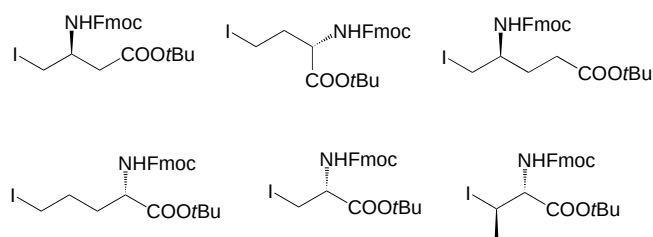
There have been few reports of libraries that contain A<sub>2</sub> GAAs. One of the problems associated with sugar mimetics that incorporate an  $\alpha$ -amino acid moiety at the



Scheme 17. Synthesis of a glycoside library of thiosugar amino acids (P = hydrophobic tag).<sup>[107]</sup>

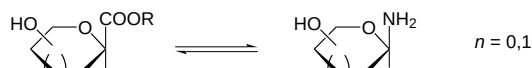


I-AA:



Scheme 18. Synthesis of S-glycosamino acid building blocks in the solid phase (TFA = trifluoroacetic acid, AA = amino acid).<sup>[52]</sup>

anomeric position is their tendency to equilibrate between two different stereoisomers (Scheme 19).<sup>[73, 74, 76, 82, 86]</sup> Acylation of the amine usually prevents this equilibration and the pure



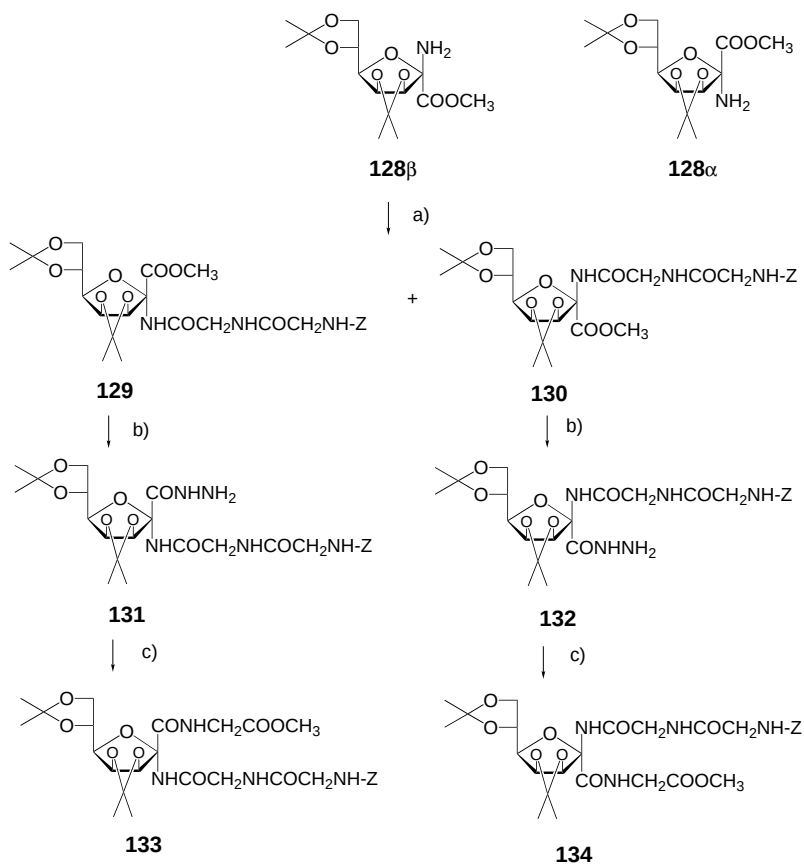
Scheme 19. Equilibration of an  $\alpha$ -amino acid incorporated in the anomeric center of carbohydrates.

stereoisomers can be isolated.<sup>[82, 86]</sup> On the other hand, strongly basic conditions afford epimerized products.<sup>[74, 75, 86]</sup> Fleet and co-workers have studied the incorporation of the mannofuranose-based aminoester **128 $\alpha$**  and **128 $\beta$**  into tri- and tetrapeptides (Scheme 20).<sup>[86]</sup> Coupling of **128 $\beta$**  with benzoyloxycarbonyl-protected Gly–Gly dipeptide afforded a mixture of tripeptides **129** and **130** in a ratio of 5:1. Extension of the tripeptide **129** at the C-terminus was effected by initial treatment with hydrazine hydrate and subsequent conversion into the acyl azide, followed by treatment with glycine methyl ester to give tetrapeptide **133**. Similar transformations of compound **130** gave the epimeric peptide **134**. Interestingly, no evidence of any epimerization at the anomeric center was found during any of the transformations after the initial acylation of the amino esters

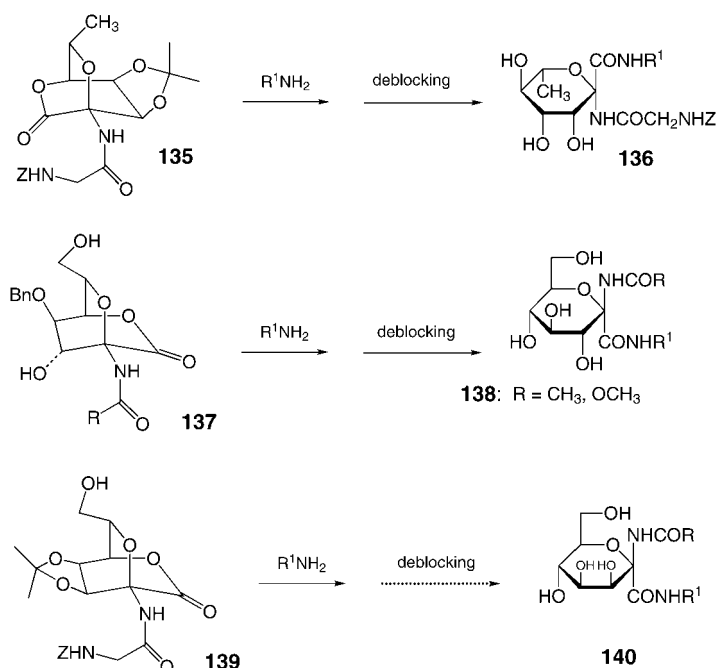
**128 $\beta$** . In contrast, separate treatment of **128 $\alpha$**  and **128 $\beta$**  with phenylisocyanate afforded configurationally pure ureas. Presumably, the increased rate of urea formation relative to amide formation prevents equilibration of the amino esters **128 $\alpha$**  and **128 $\beta$** . To synthesize epimer-free glycopeptides with incorporated anomeric  $\alpha$ -amino acids, Fleet and co-workers treated bicyclic L-rhamnolactone **135**,<sup>[156]</sup> D-glucolactone **137**,<sup>[156]</sup> and D-mannolactone **139**<sup>[84]</sup> with primary amines to yield the tripeptides **136**, **138**, and **140**, respectively, after deprotection (Scheme 21). This approach, once implemented in a combinatorial strategy, may lead to novel glycopeptidomimetics.

#### 4.7. Combinatorial Approaches Towards A<sub>3</sub> and A<sub>4</sub> GAAs

Branched A<sub>3</sub> GAAs are difficult to synthesize and have thus not been described often, and appear to have been incorporated only into short peptide sequences.<sup>[89]</sup> A<sub>4</sub> GAAs are formed by coupling an amino acid with a sugar scaffold through the amino function. Although no libraries with this building block have appeared so far, a few strategies with the potential for combinatorial application have been reported.<sup>[158–161]</sup> Among the possible A<sub>4</sub> structures, the 4-amino-4-deoxysugar skeleton, a potential antifungal and antibacterial

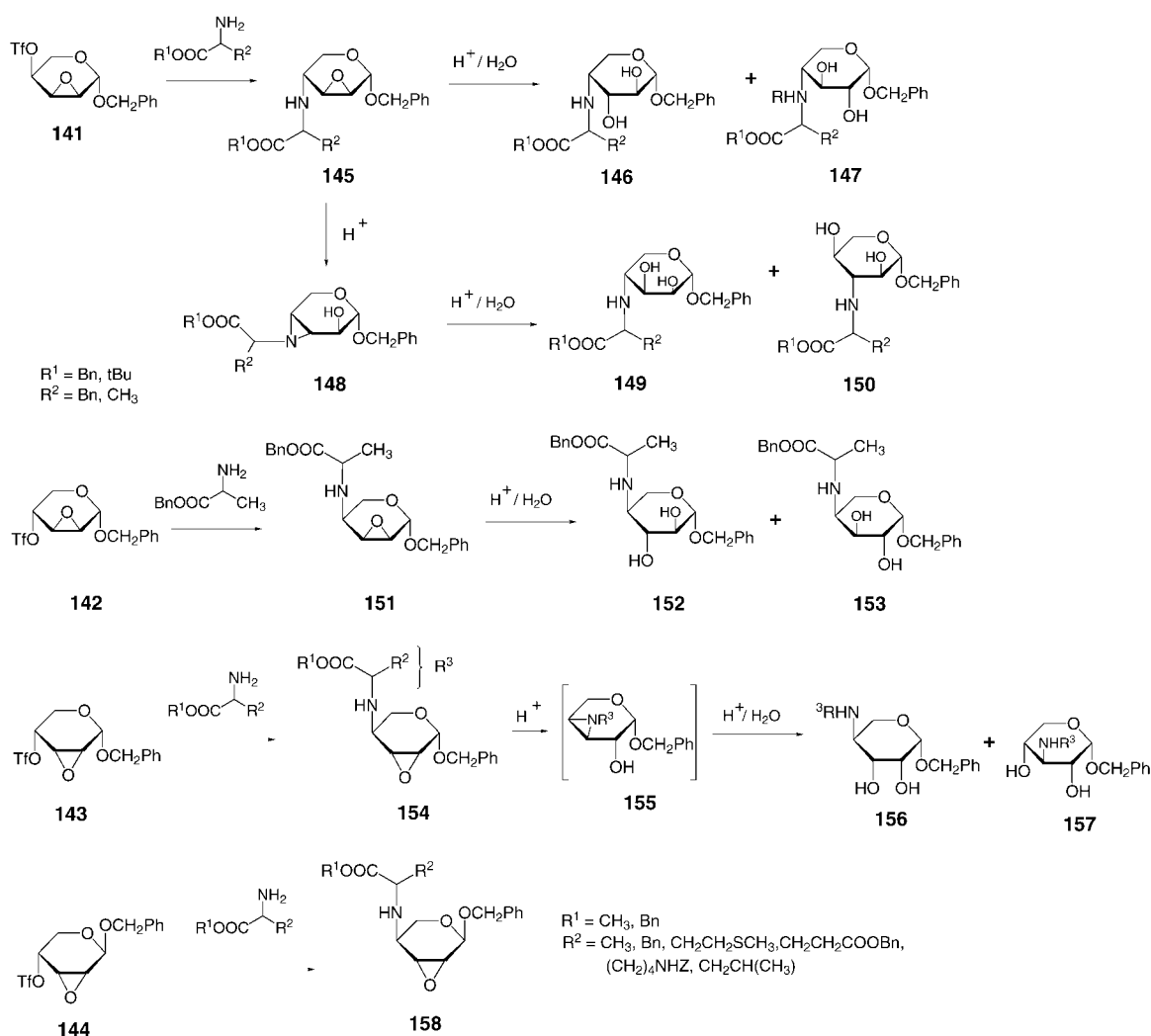


Scheme 20. Incorporation of an A<sub>2</sub> GAA into short peptides. Reagents and conditions: a) Z-NHCH<sub>2</sub>CONHCH<sub>2</sub>COOH, DCC, HOBT; b) NH<sub>2</sub>NH<sub>2</sub>, MeOH; c) *t*BuONO, HCl; then Cl<sup>−</sup>NH<sub>3</sub><sup>+</sup>CH<sub>2</sub>COOCH<sub>3</sub>, Et<sub>3</sub>N (DCC = dicyclohexylcarbodiimide, HOBT = 1-hydroxy-1*H*-benzotriazole).



Scheme 21. Lactone strategy to incorporate an  $A_2$  GAA into short peptides ( $Z$  = benzyloxycarbonyl).

agent,<sup>[157]</sup> and the 2-amino-2-deoxysugar skeleton, a common building block in glycoconjugates such as peptidoglycans, mucopolysaccharides, bacterial lipopolysaccharides, antigens, and blood group substances, have attracted some interest.<sup>[158–161]</sup> Voelter and co-workers<sup>[158]</sup> investigated the substitution of the triflate group in 2,3-anhydro-4-*O*-trifluoromethanesulfonyl glycosides **141–144** by amino esters as a method to prepare sugar amino acid conjugates (Scheme 22). By using this strategy, it was possible to incorporate a variety of amino acid derivatives into the sugar scaffold. Treatment of triflate **141** with the free amine of alanine, phenylalanine, or *tert*-butyl 4-aminobenzoate provided epoxide **145**. Subsequent acid-catalyzed epoxide opening in an aqueous solution afforded diols **146** and **147**. Exposure of epoxide **145** to silica gel yielded aziridine **148** quantitatively which was converted into diols **149** and **150** by acid hydrolysis. Analogously, treatment of triflates **142**, **143**, and **144** with amino acid derivatives provided the corresponding sugar–amino acid conjugates **151**, **154**, and **158** in 60% average yield. Solvolysis of *trans*-amino epoxide **154** furnished diols **156** and **157**, presumably via aziridine intermediate **155**. Similarly, hydrolysis of **151** afforded GAA derivatives **152** and **153** (Scheme 22).



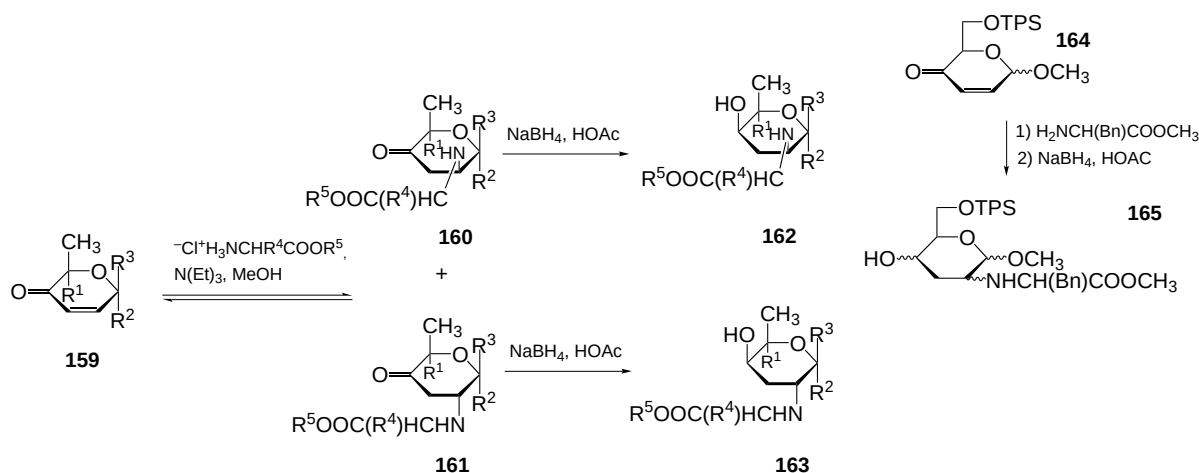
Scheme 22. Synthesis of  $A_4$  GAAs by substitution of the triflate group (TfO) with amino acids (Bn = benzyl).

A Michael addition approach towards the synthesis of 2-amino-2,3-dideoxy-GAAs was described by Georgiadis and co-workers (Scheme 23).<sup>[159–161]</sup> The 2,3-dideoxy-hex-2-enopyranos-4-ulose **159** reacted with a variety of amino esters to yield the corresponding unstable Michael adducts **160** and **161**. Subsequent reduction of the ketone afforded the stable amino acid conjugates **162** and **163**. A similar reaction sequence on **164** provided the GAA **165**.

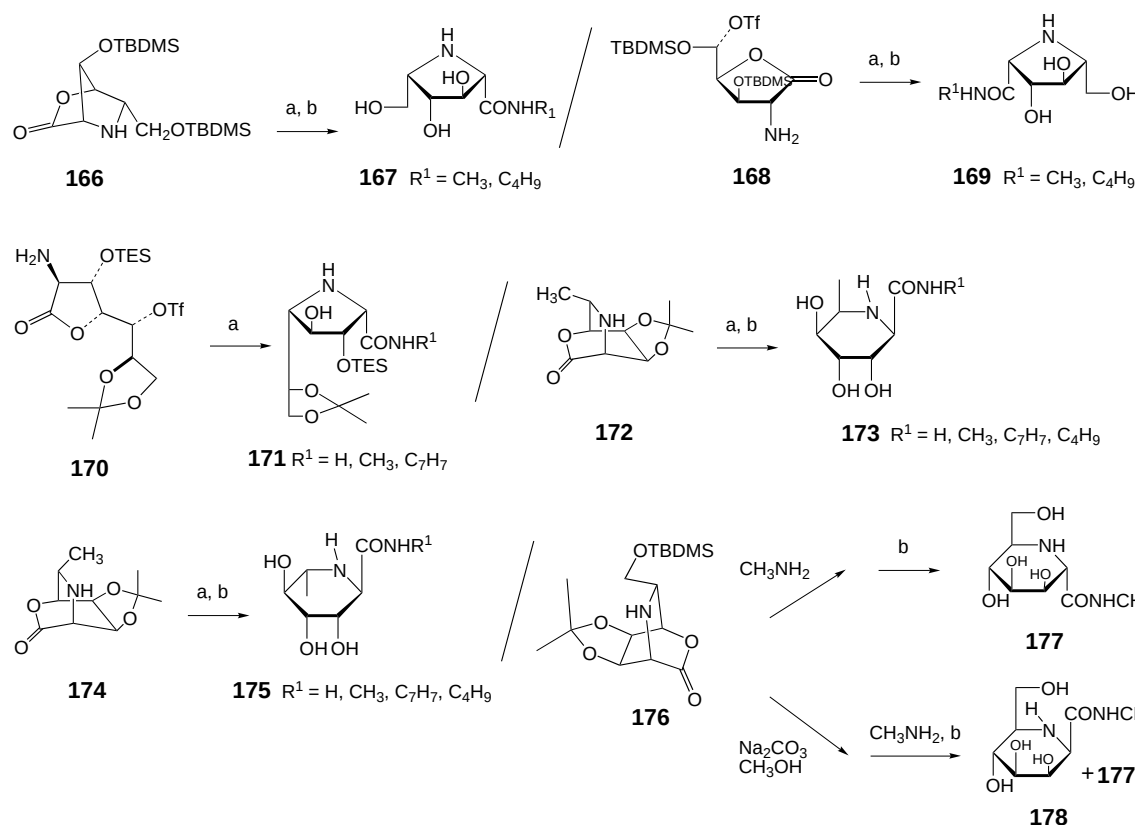
#### 4.8. Access to Azasugar Acid Libraries

Among the azasugar amino acids, the proline derivatives and pipecolic acids have attracted considerable interest over

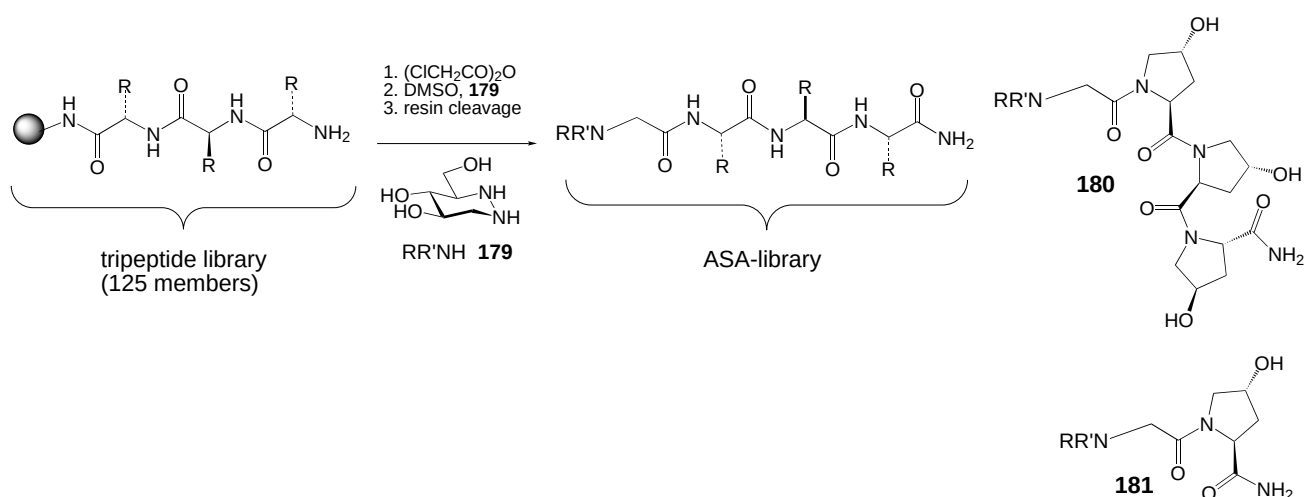
the years as a result of their potential to induce secondary structures in peptides and their potential as glycosidase inhibitors. Fleet and co-workers reported a lactone strategy that can be used to incorporate proline and pipecolic acids into azasugar libraries (Scheme 24).<sup>[101, 102, 104, 162]</sup> Treatment of the lactones **166**, **168**, and **170** with primary amines and subsequent deprotection, if necessary, provided the corresponding hydroxyproline derivatives **167**,<sup>[162]</sup> **169**,<sup>[162]</sup> and **171**.<sup>[104]</sup> Similarly, the pipecolic acids **173**,<sup>[102]</sup> **175**,<sup>[102]</sup> **177**,<sup>[101]</sup> and **178**<sup>[101]</sup> were accessible from the bicyclic lactones **172**, **174**, and **176** (Scheme 24). Interestingly, the ASA-derivatives **177** and **178** showed strong competitive inhibition of  $\beta$ -N-acetylglucosaminidases from bovine liver and human placenta.<sup>[101]</sup>



Scheme 23. Michael addition approach towards  $A_4$  GAAs (TPS = triphenylsilyl).  $\text{R}^1 = \text{C}_6\text{H}_5$  or  $\text{C}_6\text{H}_4\text{SO}_2\text{C}_6\text{H}_5$ ;  $\text{R}^2 = \text{OCH}_3$  or H;  $\text{R}^3 = \text{H}$  or  $\text{CH}_3$ ;  $\text{R}^4 = \text{H}$  or  $\text{CH}_3$  or Bn;  $\text{R}^5 = \text{CH}_3$  or  $\text{CH}_2\text{CH}_3$ .



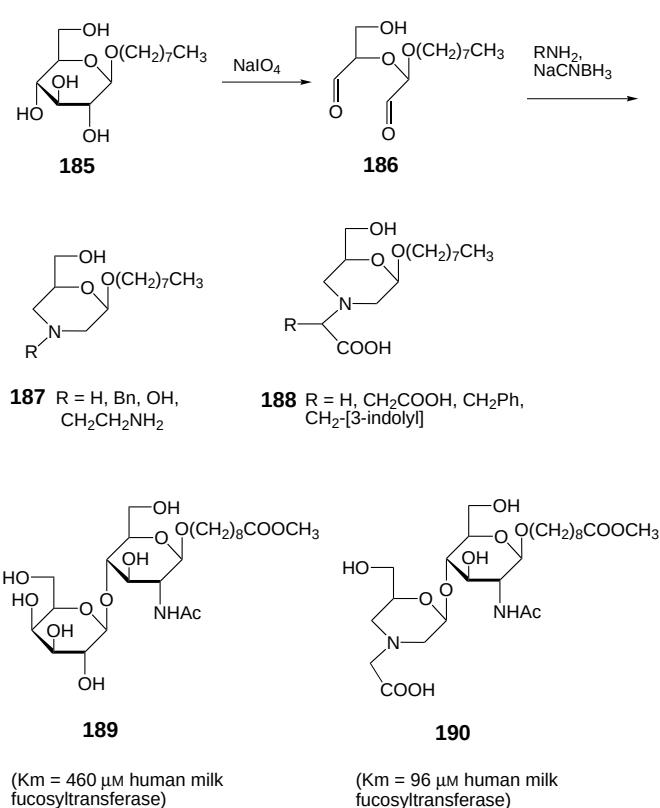
Scheme 24. Lactone strategy to prepare derivatives of  $A_5$  GAAs (TBDMS = *tert*-butyldimethylsilyl). a)  $\text{R}^1\text{NH}_2$ , b) deprotecting.

Scheme 25. Synthesis of an ASA library designed to interact with glycosidases.<sup>[163, 164]</sup>

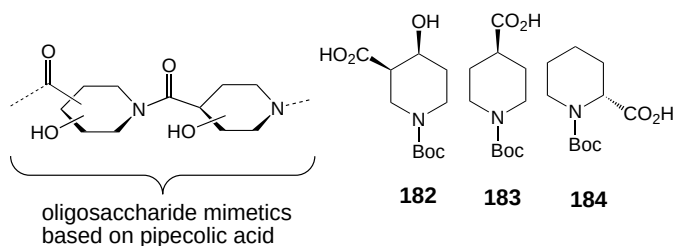
A library of azasugar glycosidase inhibitors was prepared recently by Bols and co-workers (Scheme 25).<sup>[163, 164]</sup> Initially, a tripeptide library that consisted of the L-amino acids of threonine, serine, 4-hydroxyproline, phenylalanine, and alanine was synthesized in the solid phase (4-methylbenzhydrylamine resin) by using the split-and-mix method. Subsequently, the resulting five sub-libraries of 25 peptides in each reactor were treated individually with chloroacetic anhydride followed by substitution with the azasugar azafagomine (**179**) and cleavage from the resin. Deconvolution of the most active sub-libraries yielded the potent inhibitor **180** for  $\beta$ -glucosidase from almonds ( $K_i = 40 \mu\text{M}$ ). All the peptide positions of **180** have hydroxyproline substituents. Interestingly, this compound was 40 times more active than **181**, but still 60 times less active than the unmodified azafagomine, which indicates that the triproline residue contributed to binding. Most compounds in this library also inhibited glycogen phosphorylase.

A small 27-membered amide library of piperidine-based carbohydrate mimics were synthesized in the solid phase.<sup>[165]</sup> A split-and-mix synthesis with building blocks **182**, **183**, and **184** (Scheme 26) afforded 27 trimers, which were subsequently tested for activity against  $\alpha$ -glucosidase (yeast),  $\beta$ -glucosidase (almonds), isomaltose (yeast),  $\alpha$ -fucosidase (human placenta),  $\beta$ -mannosidase (snail), and  $\beta$ -galactosidase (*E. coli*). Unfortunately, none of the enzymes were inhibited significantly by the library compounds.

Hindsgaul and co-workers developed a short pathway to morpholine-based SAAs (Scheme 27).<sup>[166]</sup> Periodate oxidation

Scheme 27. Synthesis of morpholine-based GAAs.<sup>[166]</sup>

tion of the octylglucoside **185** affords dialdehyde **186**, which can be purified easily by simple adsorption onto reverse-phase C-18 resins. Reductive amination of **186** with a variety of amines (benzylamine, hydroxylamine, unprotected amino acids) affords morpholine-based ASAs **187** and **188**. The reaction was extended to the N-acetyllactosamine derivative **189**, in which only the terminal Gal residue contains vicinal diols. Periodate oxidation followed by reductive amination with glycine gave the 3'-azadisaccharide derivative **190**. Interestingly, the disaccharide mimetic **190** was a better substrate than **189** for human milk fucosyltransferase (Scheme 27).

Scheme 26. Synthesis of a library of amides designed as oligosaccharide mimetics. The library is based on pipercolic acid building blocks.<sup>[165]</sup>

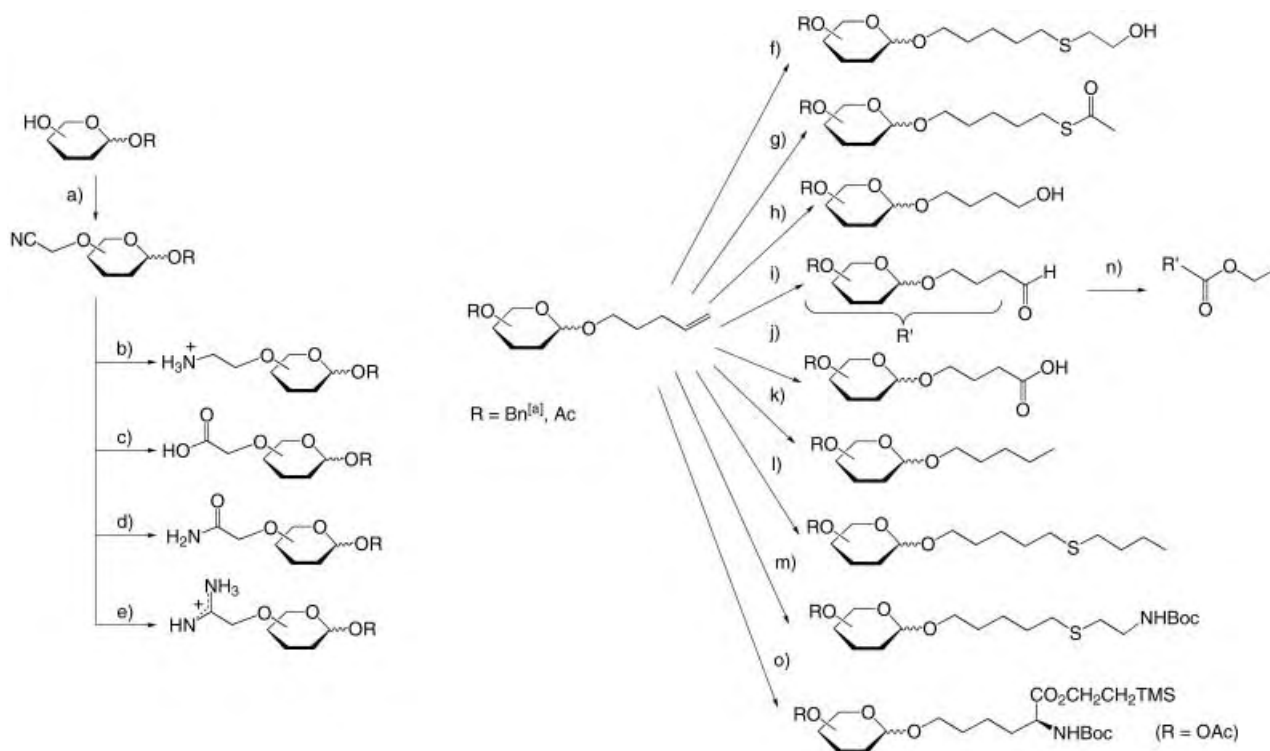
## 5. Synthetic Operations on the Polyol Platform Designed to Increase Functional Diversity of GAAs

Although carbohydrate scaffolds are highly functionalized building blocks, their functional diversity is limited to the presence of primary and secondary hydroxy groups. To increase the functional diversity of the sugar platform, easy, high-yielding transformations of the alcohol function into derivatives is required. So far, most of the previous work in this article has dealt with the conversion of alcohols into esters, ethers, carbamates, and carbonates. Furthermore, activation of the hydroxy group as activated esters has been used to incorporate amines, amino acids, azides,<sup>[167]</sup> and thiols<sup>[155]</sup> into the sugar scaffold by nucleophilic substitution. Nucleophilic displacement of activated primary hydroxy functions usually proceeds easily, whereas secondary hydroxy groups require more drastic conditions and therefore are subject to side reactions. Recently, hypervalent silicate intermediates were used as efficient nucleophilic azide or cyanide sources to undergo rapid and efficient azide displacement reactions with primary and secondary alkyl halides and sulfonates.<sup>[94]</sup> Alternatively, additional diversity may also be introduced through functionalized tethers.<sup>[168, 169]</sup> Hindsgaul and Malet<sup>[168]</sup> derivatized mono- and disaccharides with the O-cyanomethyl group, which is a versatile precursor for a variety of functional groups including carboxylic acids, amines, amides, and amidines (Scheme 28). O-pentenyl glyco-

sides can also be easily converted into novel structures under mild conditions (Scheme 28).<sup>[169, 172]</sup> Similar conversions can also be envisaged with O-allyl ethers of sugars.<sup>[170, 171]</sup>

## 6. Summary and Outlook

GAAs are versatile building blocks for combinatorial synthesis (for examples, see Table 1 and relevant tables in the Supporting Information). Derivatization and oligomerization of the amino acid moiety has been used to generate simple glycomimetic libraries. Biological evaluation of these compounds has resulted in the discovery of potent inhibitors of carbohydrate–protein binding. Besides being sugarlike, GAAs are also potential peptidomimetics. SAA-based dipeptide isosteres have been incorporated into short peptide sequences, which were shown to be biologically active. Finally, the rich stereochemistry and high degree of functionalization of GAAs may result in their use as scaffolds for the construction of pharmacophore groups. Combinatorial derivatization of the polyol moiety of GAAs as esters, ethers, carbonates, or carbamates by orthogonal protection<sup>[141, 142]</sup> may lead to structures with new pharmacological properties. Because of the wide implications of peptides and carbohydrates in many diseases<sup>[31]</sup> and as building blocks for biopolymers, GAAs hold great promise for drug discovery and materials science.



Scheme 28. Ether- or glycoside-based tethers attached to the carbohydrate platform can be used to increase the functional diversity of the polyol scaffold.<sup>[168, 169, 172]</sup> Reagents and conditions: a) NaH, BrCH<sub>2</sub>CN, CH<sub>3</sub>CN; b) BH<sub>3</sub>·Me<sub>2</sub>S, THF, reflux; c) NaOH, MeOH, reflux; d) NaOMe/MeOH, 12 h, room temperature, then NaHCO<sub>3</sub>; e) NaOMe/MeOH, 12 h, room temperature, then NH<sub>4</sub>Cl; f) HOCH<sub>2</sub>CH<sub>2</sub>SH, AIBN, dioxane, Δ; g) CH<sub>3</sub>COSH, AIBN, dioxane, Δ; h) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, then BH<sub>3</sub>·Me<sub>2</sub>S or NaBH<sub>4</sub>; i) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, then BH<sub>3</sub>·Me<sub>2</sub>S; j) RuCl<sub>3</sub>/NaIO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN/H<sub>2</sub>O (2:2:3); k) H<sub>2</sub>, Wilkinson's catalyst, EtOAc; l) CH<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>SH, AIBN, dioxane, Δ; m) HSCH<sub>2</sub>CH<sub>2</sub>NHBoc, AIBN, dioxane, Δ; n) NaH, (EtO)<sub>3</sub>P(O)CH<sub>2</sub>COOEt, THF, 0 °C; o) 1. O<sub>3</sub>, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, pyridine, Me<sub>2</sub>S; 2. tetramethylguanidine, THF, -78 °C → RT, P(OMe)<sub>2</sub>(O)CH(NHBoc)CO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>TMS; 3. (S,S)-Et-DuPHOS-Rh<sup>+</sup>, THF, room temperature, H<sub>2</sub> (50 psi); [a] except for o. (AIBN = azobisisobutyronitrile, Et-DuPHOS = 2',5'',5'')-tetraethyl.

## Abbreviations:

|      |                   |
|------|-------------------|
| AA:  | amino acid        |
| GAA: | glycosamino acid  |
| GNA: | glyconucleic acid |
| SAA: | sugar amino acid  |
| Ur:  | uridine           |

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# The “Correctly Folded” State of Proteins: Is It a Metastable State?

Ehud Gazit\*

Infectious, genetic, and sporadic protein misfolding diseases are currently of a major medical, social, and even political concern. Such concern calls for a fresh consideration of the central dogmas of the field of protein folding. Experimental data indicate that concentrated aqueous solutions of numerous disease-related but also generic proteins undergo spontaneous aggregation. Such aggregation is associated with a structural transition from the “correctly folded” state of the proteins into a collapsed  $\beta$ -sheet-rich structure. The process of protein aggregation is often thermodynamically irreversible and the large aggregates formed are very stable. These observations and others leads us to suggest that the aggregated form of proteins may represent a true global minimum of free-energy for ensembles of protein molecules in general and not for aggregation-prone proteins only. In line with this hypothesis, the situation of an ensemble of “correctly folded” proteins in solution may represent a kinetically-trapped metastable state. We hypothesize that at an infinite time any protein solution above a critical concentration will eventually undergo structural transition into the aggregated state.

## Introduction

There has been an increasing interest in the study of protein misfolding and aggregation in recent years.<sup>[1]</sup> There are two main reasons for this: 1) The sharp increase in the occurrence of genetic and sporadic amyloidosis and other protein-misfolding diseases, many of which are correlated with the increased life expectancy of the western population. 2) The outbreak of a major infectious protein-misfolding disease, bovine spongiform encephalopathy (BSE), also known as the mad cow disease.

We currently know of more than twenty unrelated protein-misfolding diseases.<sup>[1]</sup> A partial list of such diseases includes Alzheimer's disease, type II diabetes, Creutzfeldt–Jakob disease (CJD), and various unrelated forms of amyloidosis. Although these diseases are of unrelated origin, they all share several biochemical and biophysical properties. In each case there is a progressive transition of normal, correctly folded cellular proteins into an aggregated state. In the aggregated

state the proteins undergo a major structural change from their normal secondary structure into a  $\beta$ -sheet-rich conformation. Usually protein-misfolding diseases are spontaneous ones. For some unknown reason, at a certain stage, mostly in old age, normal proteins are transformed into the pathological aggregated state. In a minority of the cases there is a genetic background in which the proteins prone to aggregation have a different amino acid sequence than the corresponding normal proteins in the population. Such mutations lead to an early onset of the misfolding diseases. Examples for genetic factors are the Flemish mutation in the  $\beta$ -amyloid ( $\beta$ A) peptide, which results in an early manifestation of Alzheimer's disease;<sup>[2]</sup> the Japanese mutation in the islet amyloid polypeptide (IAPP), which causes an early onset of type II diabetes;<sup>[3]</sup> and the mutations in the PrP protein that lead to the inherited spongiform encephalopathy forms of CJD, Gerstmann–Straussler–Scheinker disease, or atypical dementia.<sup>[4]</sup>

Infectious protein diseases or prion diseases are directly linked to the spontaneous and genetic protein-misfolding diseases.<sup>[4]</sup> Actually, BSE is the infectious form of the spontaneous or inherited CJD. In BSE, the infecting agent is an aggregate of cellular PrP proteins that have undergone structural transition into the infectious Pr(Sc) form. This aggregate of Pr(Sc) interacts with normal, correctly folded PrP cellular proteins and causes an irreversible transition of the latter into the aggregated and misfolded state.

These two forms of protein-misfolding diseases, the spontaneous and the infectious, not only have an enormous medical and social impact; they also raise significant doubts regarding the central dogma of the protein folding field, as is discussed below. The epidemic of BSE in Europe made very clear that infectious protein-misfolding diseases are also a major economical and political matter. Better mechanistic understanding of the aggregation process is needed since, unlike for other major diseases, gene therapy will not be a very useful way to solve protein-misfolding maladies. The interesting fact in all cases of misfolding diseases, from the thermodynamic point of view, is the irreversibility of the aggregation process and the exceptional stability of the aggregates. Actually, the extraordinary stability of the prion infectious agent causes a significant medical problem. The protein aggregates are resistant to disaggregation by disinfecting agents, a situation that raises a major worry regarding the possibility of infection of patients by contaminated surgical and dental tools.<sup>[5]</sup>

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# The "Thermodynamic Theory" of Protein Folding

The central dogma of the protein folding field was put forward by Chris B. Anfinsen more than forty years ago.<sup>[6]</sup> The basic premise of this theory, labeled the thermodynamic theory, stresses that the energetically favored state of proteins is their "correctly folded" one. In a series of very elegant experiments, Anfinsen and his colleagues proved that all the information needed for a protein to be folded correctly is contained within its primary structure. Moreover, an unfolded protein will spontaneously fold to its correctly folded form, which is the state of the lowest Gibbs energy for a given protein. For this theory Anfinsen was awarded the Nobel Prize in Chemistry in 1972. While it is presumably true that the correctly folded state is the state of lowest Gibbs energy for a given isolated protein molecule—that is, in an infinitely diluted solution as explicitly assumed by Anfinsen's model (see below)—experimental evidence raises doubt as to whether this is valid for concentrated ensembles of proteins in aqueous solution.

## Experimental Studies of Protein Aggregation

It is well known that concentrated aqueous solutions of numerous unrelated proteins undergo aggregation, and this process was studied extensively.<sup>[1]</sup> The aggregation process is normally composed of two parts (Figure 1). The first step is a

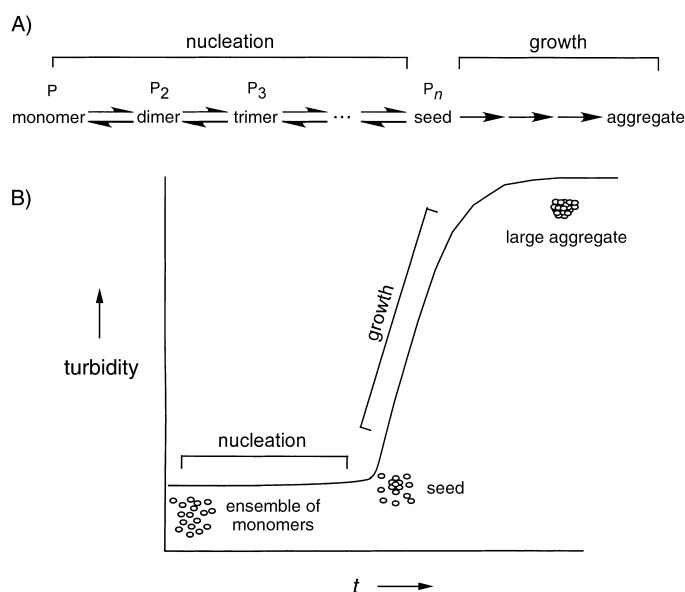


Figure 1. A) The mechanism of protein aggregation involves two stages: A nucleation process is followed by growth of the nuclei to a critical mass. B) A typical aggregation curve. Aggregation is usually determined by monitoring the turbidity of the solution as a function of time. The required initial nucleation results in a delayed appearance of solution turbidity.

reversible nucleation. At this stage proteins are sequentially added to a growing nucleus in a thermodynamically reversible manner. The second part of the process occurs after the growing nucleus reaches a critical mass. Then there are further irreversible additions of protein molecules to the nucleus. This eventually leads to the formation of a large aggregate. The aggregates are very stable, and there is no evidence for an

equilibrium between the aggregated state and the correctly folded state.

It is very interesting that not only disease-related proteins undergo aggregation in solution. It was also observed that disease-unrelated proteins—such as the SH3 domain, myoglobin, and a bacterial cold shock protein—form aggregated structures in solution.<sup>[7]</sup> One of the generic types of aggregates formed by unrelated proteins is amyloid fibrils. These fibrils are presumably built by intermolecular backbone hydrogen bonding interactions.<sup>[7]</sup> These observations led to the suggestion that the aggregated form, and most notably the amyloid form, may represent a generic form of protein.<sup>[1]</sup> Moreover, non-amyloid aggregated structures are also extremely interesting since this aggregated state may be the actual agent that causes cell death.<sup>[8]</sup> It is also common for any person studying protein chemistry to witness that concentrated protein preparations eventually aggregate and precipitate after long storage.

## The Effect of Chemical Chaperons

Chemical chaperons are small molecules that have a very robust effect on the thermodynamic stability of various unrelated proteins.<sup>[9]</sup> The list of chemical chaperons includes naturally occurring organic osmolytes as well as solvents. Chemical chaperons are assumed to change the thermodynamic landscape of proteins by controlling protein folding through a preferential hydration of the exposed polypeptide backbone and side chains of partially unfolded structures.

A chemical chaperon with a remarkable ability to affect protein folding is trimethylamine *N*-oxide (TMAO). The claim is that agents like TMAO can "force thermodynamically unfolded proteins to fold".<sup>[9]</sup> Unlike helix-promoting solvents such as trifluoroethanol, TMAO does not seem to favor a particular form of secondary structure. It was recently shown that TMAO can manipulate in vitro the aggregation state of the  $\beta$ -amyloid peptide involved in Alzheimer's disease.<sup>[10]</sup> Upon addition of TMAO there was a dose-dependent increase in the aggregation of the peptide.<sup>[10]</sup> We observed that this same effect of TMAO is true for a variety of unrelated proteins (unpublished results). Therefore, the same agent that forces proteins to fold into the correctly folded state also causes protein aggregation. Our molecular explanation for this phenomenon is that in the same manner that TMAO forces proteins into the folded state, it further forces them into the aggregation state by overcoming energy barriers.

## The "Metastability Theory" of Protein Folding

The combination of the issues raised above led us to suggest a new way to consider the thermodynamics of protein misfolding. Our approach diverts from the traditional view of each isolated protein molecule as an independent thermodynamic system, but considers the ensemble of proteins in aqueous solution as one large thermodynamic system (Figure 2). According to this view, a solution of proteins that are prone to aggregation but correctly folded represents a system in a transient state that will eventually reach the global Gibbs energy minimum of the aggregated state. The fact that many

generic proteins undergo similar aggregation processes calls for an expansion of the model. It seems to be that many proteins will sooner or later undergo aggregation. For some proteins this may take minutes or hours and for others it can take days or months. We hypothesize that at infinite time *any* protein solution above a critical concentration  $C_{ag}$  will eventually undergo structural transition into an aggregated state. The exact value of  $C_{ag}$  varies from one type of protein to the other and is also dependent on parameters such as temperature, ionic strength, and pH. To test this model and to understand protein aggregation as a generic process, future research should be conducted not only for hours and days (as is done, for example, for the  $\beta A$  peptide), but also for weeks or months.

The important point is that the thermodynamically favored state of an ensemble of proteins is likely to be the aggregated

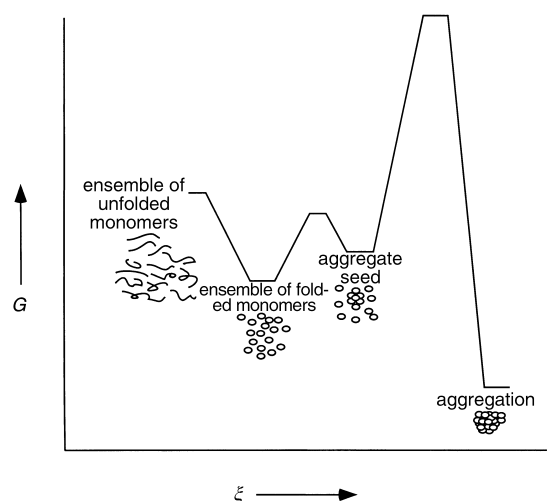


Figure 2. A model for the aggregation of proteins in which the ensemble of proteins in aqueous solution is viewed as one thermodynamic system. Shown is the relative Gibbs energy of unfolded, folded, pre-aggregated, and aggregated proteins. The aggregated state represents the global minimum of Gibbs energy. However, the large activation energy kinetically traps the proteins of the ensemble in the correctly folded state.  $G$  = Gibbs energy,  $\xi$  = reaction coordinate.

or misfolded one. In line with this model, a concentrated solution of correctly folded proteins represents a metastable state. A classical definition of a metastable state is a state of a local minimum that is isolated from the global minimum by an energy barrier and is hence maybe kinetically trapped. Therefore, in spite of the fact that the metastable state is only a local minimum and not the global minimum of the system, for practical reasons in some cases it is the state observed for a considerable amount of time.

Indeed, some experimental data hints that the transition from the correctly folded state to the global minimum of the aggregated state is achieved by overcoming an energy barrier. Often heating a protein solution causes rapid aggregation. The common explanation for this is that heating causes partial unfolding of the proteins, and the partial unfolding accelerates aggregation. However, this is in contrast to the observation that chemical chaperons, which inhibit partial unfolding,

actually accelerate the aggregation process. We speculate that in fact heating helps the protein solution to overcome the large energy barrier separating the aggregated state from the kinetically trapped correctly folded state. In the same manner, chemical chaperons, which force proteins into the folded state, further force them into the aggregation state by overcoming such large energy barriers.

### Conclusion

Protein misfolding is a major medical, economical, and even political issue. This leads to the need for a fresh view on protein folding with an emphasis on the misfolded state. While it is true that for isolated protein molecules the correctly folded state is the state of the lowest Gibbs energy, this is apparently not the case for an ensemble of many protein molecules in solution. All the experimental evidence leads to the conclusion that for many proteins the favorable state or the state of the lowest Gibbs energy is the aggregated one. We speculate that this is true for all proteins. Therefore, the correctly folded state of any generic protein ensemble may be a local minimum of Gibbs energy. If this is true, at an infinite time all proteins will be transformed to an aggregated state.

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# Coordinative Unsaturation in Platinum(IV) Chemistry: From Proposed Reaction Intermediates to the First Structurally Characterized Complexes\*\*

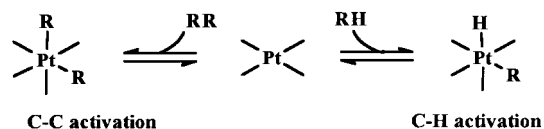
Richard J. Puddephatt\*

Coordinatively unsaturated intermediates are recognized to be important in homogeneous catalysis and bond activation using transition metal complexes, as was most explicitly stated in Tolman's 16- and 18-electron rule.<sup>[1]</sup> However, direct proof of 16-electron platinum(IV) complexes has been difficult to come by and only recently have two papers been published that describe structural characterization of such compounds.<sup>[2, 3]</sup> Herein some of the history in highlighting the new breakthroughs is summarized.

Classical Werner-type platinum(IV) complexes, such as  $[\text{PtCl}_6]^{2-}$  or  $[\text{PtCl}_4(\text{NH}_3)_2]$  are invariably octahedral with 18-electron configurations, and they are inert towards ligand-substitution reactions. Ligand dissociation to give 16-electron intermediates must therefore be very difficult in these compounds and, to avoid this step, most substitution reactions occur by redox mechanisms. The reactions often involve catalysis, and overall substitution at platinum(IV) occurs by atom transfer or by substitution in transient platinum(II) or platinum(III) intermediates. These conclusions were drawn based on pioneering research on inorganic reaction mechanisms beginning in the 1950's, as summarized in the classic text by Basolo and Pearson.<sup>[4]</sup> There is naturally some controversy when such conventional wisdom is challenged.

## 16-Electron Platinum(IV) Complexes as Reaction Intermediates

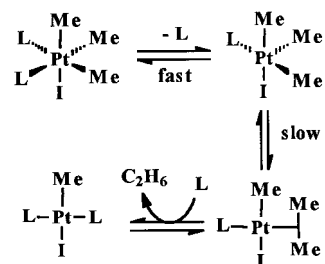
The study of alkyl and hydrido complexes of platinum(IV) was spurred on by the discovery of the activation of alkanes by platinum(II) complexes in 1969 by Shilov and co-workers, in which alkyl or alkyl(hydrido) complexes of platinum(IV) were suggested as key intermediates (Scheme 1).<sup>[5]</sup> The key reaction is the activation of C–H (or, in principle, C–C bonds, though this is possible only in very special cases, such as in strained cyclopropane derivatives) by concerted *cis* oxidative addition to platinum(II) centers of C–H (or C–C) bonds.



Scheme 1. Activation of alkanes (R = alkyl) by platinum(II) species; C–H activation is much easier than C–C activation.

However, the catalytic systems were then too complex to allow study of the individual steps.<sup>[5, 6]</sup>

At that time alkylplatinum(IV) compounds were already known, and the reductive elimination to form platinum(II) compounds by C–C bond reductive elimination was established.<sup>[7]</sup> Since this is the microscopic reverse of the alkane activation step of Scheme 1, the mechanism of the reductive elimination was studied. The reductive elimination of ethane from *fac*- $[\text{Pt}(\text{Me})_3\text{L}_2]$ , L = tertiary phosphane ligand, was strongly retarded in the presence of free ligand L, and it was suggested that the reaction occurred by loss of a phosphane ligand to give a 16-electron intermediate  $[\text{Pt}(\text{Me})_3\text{L}]$  from which the key reductive-elimination step occurred through a C–C  $\sigma$ -bond complex transition state (Scheme 2).<sup>[8]</sup>



Scheme 2. Mechanism of C–C bond reductive elimination from platinum(IV) centers.

From Scheme 2 it can be deduced that the reductive elimination would be more difficult with ligands L that could not easily dissociate, and it was shown that these reactions are much more difficult with chelating diphosphane ligands.<sup>[8]</sup> On the other hand, if the reverse alkane activation is to be achieved, the alkane must displace L from the platinum(II) center in the first step and so at least one very labile ligand should be present. A T-shaped 14-electron platinum(II) complex would be ideal, and such unsaturated intermediates are

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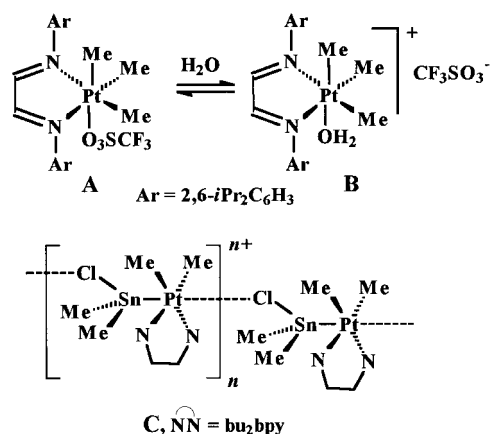
now also established as reaction intermediates.<sup>[9]</sup> Why are the Werner complexes and organometallic complexes different? The key factor is that strong  $\sigma$ -donor groups hydride or alkyl, and also related groups such as silyl or stannyl, have a very strong *trans*-influence<sup>[10]</sup> that weakens and polarizes the *trans* Pt–L bond and can lead to easy ligand dissociation with formation of short-lived 16-electron platinum(IV) or 14-electron platinum(II) complexes.

Subsequent mechanistic studies have confirmed that 16-electron platinum(IV) complexes are intermediates in most reductive–elimination reactions that lead to C–H<sup>[11]</sup> or C–C<sup>[12, 13]</sup> bond formation, as well as in the opposite C–H<sup>[5, 6, 14]</sup> or C–C<sup>[15]</sup> bond activation reactions by oxidative addition to platinum(II) centers. They have also been proposed as intermediates in  $\alpha$ - or  $\beta$ -elimination reactions from alkylplatinum(IV) complexes,<sup>[16]</sup> in alkyl transfer reactions,<sup>[12]</sup> and in skeletal rearrangements of platinum(IV)cyclobutane complexes.<sup>[17]</sup>

The recent discovery of the selective oxidation of methane to methyl bisulfate by SO<sub>3</sub>, catalyzed by [PtCl<sub>2</sub>(2,2'-bipyrimidine)] has stimulated renewed interest in the alkane-activation chemistry at platinum(II) centers,<sup>[18]</sup> and in the nature of the 16-electron platinum(IV) intermediates. Several theoretical studies have indicated that these intermediates should have square-pyramidal geometry,<sup>[19]</sup> but the challenge remained to isolate such compounds and to confirm their structures experimentally.

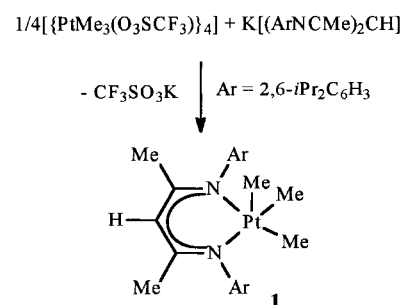
#### Synthesis of 16-Electron Platinum(IV) Complexes

The first attempts to prepare 16-electron platinum(IV) complexes were inconclusive or unsuccessful. For example, reaction of complexes [PtXMe<sub>3</sub>L<sub>2</sub>], X = halide, with silver triflate or of [PtMe<sub>2</sub>L<sub>2</sub>] with methyl triflate gave complexes, **A** or **B**, with weakly bound triflate or water molecules in the sixth coordination site when L<sub>2</sub> = ArN=CHCH=NAr (Ar = 2,6-*i*Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>) or led to reductive elimination of ethane when L<sub>2</sub> = Ph<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>PPh<sub>2</sub>.<sup>[12]</sup> The complexes **A** and **B** were in very rapid equilibrium, presumably because the 16-electron complex was very close in energy.<sup>[12]</sup> An attempt to use the very high *trans*-influence of the stannyl or silyl group to stabilize the 16-electron intermediate led to isolation of a complex [PtMe<sub>2</sub>(SnMe<sub>2</sub>Cl)(bu<sub>2</sub>bipy)][BF<sub>4</sub>] (**C**; bipy = 2,2'-bipyridine), but in the solid state it formed weak intermolecular

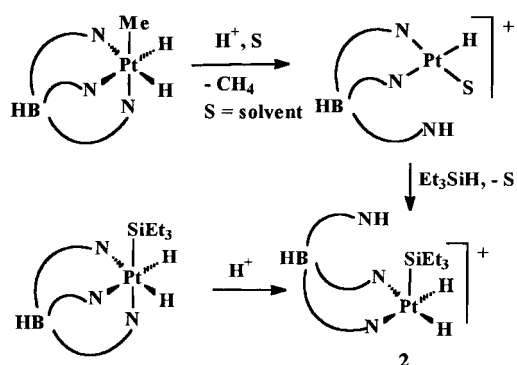


SnCl–Pt bonds at the potentially vacant site.<sup>[20]</sup> The complexes [PtMe<sub>2</sub>(MPPPh<sub>3</sub>)(bipy)]<sup>+</sup>, M = Ag or Au, were thought to be 16-electron complexes but could not be crystallized, but the perfluorophenyl complex [Pt(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>(SC<sub>4</sub>H<sub>8</sub>)(AgPPh<sub>3</sub>)] was structurally characterized.<sup>[20]</sup>

The final breakthrough occurred as the 16-electron platinum(IV) complexes [PtMe<sub>3</sub>{(NArCMe)<sub>2</sub>CH}] (**1**; Ar = 2,6-*i*Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>), and [PtH<sub>2</sub>(SiEt<sub>3</sub>)(Tp')]<sup>+</sup> (**2**; Tp' = hydridotris(3,5-dimethylpyrazolyl)borate), were prepared (Scheme 3<sup>[2]</sup> and 4.<sup>[3]</sup>) and characterized both spectroscopically and by X-ray structure determinations.



Scheme 3. A 16-electron trimethylplatinum(IV) complex.



Scheme 4. Two routes to a cationic 16-electron silyldihydrido-platinum(IV) complex.

Complex **1** has square-pyramidal geometry and is highly fluxional in solution such that the axial and equatorial methyl groups appear to be equivalent in the NMR spectrum, even at low temperature.<sup>[2]</sup> Complex **1** is thermally stable in solution at room temperature but, on photolysis, it undergoes an unusual reaction in which a methyl group is transferred from platinum to the ligand to give a platinum(II) complex [PtMe<sub>2</sub>{(NArCMe)<sub>2</sub>CHMe}].<sup>[2]</sup>

The stereochemistry of complex **2** is not determined unequivocally from the X-ray structure determination since the hydride ligands were not directly located, but a combination of the X-ray data with spectroscopic and chemical data leave little doubt that it is correct.<sup>[3]</sup> Other potential structures, such as a hydrido(silane)platinum(II) formulation [PtH(HSiEt<sub>3</sub>)(Tp')], are excluded by NMR and infrared (IR) spectroscopic data. While complex **1** has close to ideal square-pyramidal geometry, complex **2** is more distorted with angles N–Pt–Si = 120.2(1) and 126.8(1)° much greater than the ideal

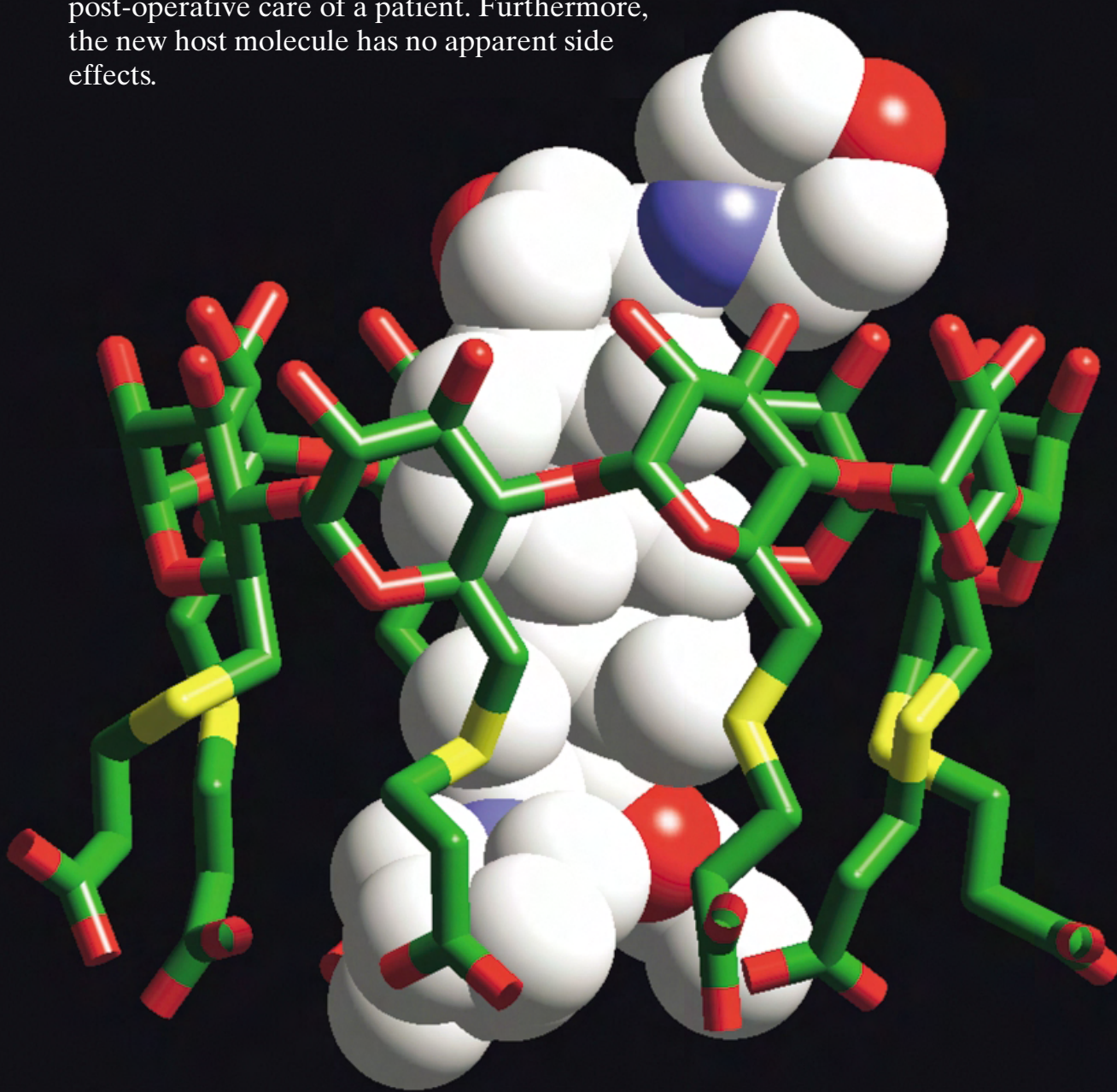
90°.<sup>[3]</sup> Similar complexes with SiPh<sub>3</sub> or SiHPh<sub>2</sub> in place of the SiEt<sub>3</sub> group in **2** were also reported.<sup>[3]</sup>

What factors allowed these remarkable 16-electron complexes **1** and **2** to be isolated? Comparison of complex **1** with the six-coordinate complexes **A** and **B**, with ligands that have similar bulky substituents, suggests that the presence of the anionic ligand giving the neutral complex **1** is the determining factor in this case. Complex **2** is cationic but the charge is well-removed from the platinum center, and the very high *trans*-influence of the silyl group as well as the presence of the bulky Tp' ligand should give extra stabilization. A whole new chemistry of the new 16-electron platinum(IV) complexes can now be expected, and the important role of these types of complexes in catalysis will be better defined by such studies.

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The steroid rocuronium, the most widely used neuromuscular blocking agent in anaesthesia, is completely encapsulated into the cavity of Org 25969, an extended  $\gamma$ -cyclodextrin host. The high affinity ( $K_a = 10^7 \text{ M}^{-1}$ ) with which Org 25969 complexes rocuronium results in it reversing the biological activities of the steroid, thus it can be used to speed up the post-operative care of a patient. Furthermore, the new host molecule has no apparent side effects.



For more  
information see the  
following pages.

## A Novel Concept of Reversing Neuromuscular Block: Chemical Encapsulation of Rocuronium Bromide by a Cyclodextrin-Based Synthetic Host\*\*

Anton Bom, Mark Bradley, Ken Cameron, John K. Clark, Jan van Egmond, Helen Feilden, Elizabeth J. MacLean, Alan W. Muir, Ronald Palin, David C. Rees, and Ming-Qiang Zhang\*

Neuromuscular blockers (NMBs, also known as skeletal muscle relaxants) are widely used during anaesthesia to facilitate endotracheal intubation and to allow surgical access to body cavities, in particular the abdomen and thorax, without hindrance from voluntary or reflex muscle movement.<sup>[1, 2]</sup> Most of these drugs achieve their effect by blocking the physiological effects of acetylcholine (ACh) at nicotinic acetylcholine receptors (nAChR) on striated muscle cells. A reversal agent is frequently administered to patients to facilitate rapid neuromuscular recovery after surgery and to prevent residual blockade.<sup>[3, 4]</sup> At present, all clinically used reversal agents, such as neostigmine, pyridostigmine, and edrophonium, are inhibitors of acetylcholinesterase (AChE). They reverse the effect of NMBs by inhibiting the breakdown of ACh, thus increasing the concentration of ACh at the neuromuscular junction. However, this increase in ACh levels induced by AChE inhibition does not remain limited to the neuromuscular junction, but also leads to nonselective activation of muscarinic acetylcholine receptors (mAChR), thus causing many side-effects, for example, bradycardia, hypotension, increased salivation, nausea, vomiting, abdominal cramps, diarrhoea, and bronchoconstriction. Therefore, in

clinical practice these drugs are usually used in combination with a mAChR antagonist such as atropine or glycopyrrolate, which themselves also have a number of side-effects, for example, dry mouth, blurred vision, tachycardia.

We hypothesized that chemical encapsulation (or chelation, complexation, sequestration) of NMBs by an exogenous host molecule would promote dissociation of NMBs from their site of action, and result in the reversal of neuromuscular blockade.<sup>[5]</sup> This mechanism of action does not involve direct interaction with cholinergic systems, and therefore, it should circumvent the undesired side-effects attendant with AChE inhibitors and furthermore eliminate the need for concomitant use of a mAChR antagonist such as atropine. We decided to investigate our hypothesis further with cyclodextrins (CDs), a group of cyclic oligosaccharides well-known for their capability to encapsulate lipophilic guest molecules such as steroids.<sup>[6]</sup> Compared with most small synthetic host molecules (including cyclophanes), CDs not only have a well-defined lipophilic cavity for host–guest complex formation, but are also generally more water soluble and biologically better tolerated.<sup>[7]</sup> In fact, several CDs have been successfully used as pharmaceutical excipients to increase water-solubility, stability, or bioavailability of lipophilic drugs.<sup>[8, 9]</sup>

The in vitro potency of the natural  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CDs to reverse rocuronium-induced neuromuscular block in isolated mouse hemi-diaphragm<sup>[10]</sup> correlates with their cavity sizes (Table 1). Only  $\gamma$ -CD, with the largest cavity size (diameter: 7.5–8.3 Å), showed reasonable reversal activity in vitro against rocuronium (concentration that is effective for 50% recovery of muscle contraction ( $EC_{50}$ ): 34.6  $\mu$ M, maximum reversal of 94.1% at 144  $\mu$ M); the  $\alpha$ - and  $\beta$ -CDs with the smaller lipophilic cavities (diameter: <6.5 Å) form less stable complexes with the bulky aminosteroid (molecule width ca. 7.5 Å). By using the NMR titration technique<sup>[11]</sup> we observed complexation-induced changes in the chemical shifts of protons from both the guest rocuronium molecule (for example, the axial methyl group (19-CH<sub>3</sub>) and H-9 $\alpha$ ) and the hosts  $\beta$ - and  $\gamma$ -CDs (for example, the internal H-3 atom). The determined association constant of  $\gamma$ -CD with rocuronium ( $K_a = 17\,000$ – $20\,400\text{ M}^{-1}$ ) by NMR titration is four- to fivefold higher than that of  $\beta$ -CD with rocuronium ( $K_a = 3500$ – $3900\text{ M}^{-1}$ ), which is consistent with their rank order in reversal potency. More detailed analysis of complexation-induced changes in the chemical shifts revealed that the protons on the steroid with the largest chemical shift changes were all located on rings A, B, and C, which indicates there is partial encapsulation of the guest.

Two strategies were adopted to increase the binding affinity of the CD host to rocuronium. The first was to extend the cavity depth of  $\gamma$ -CD in order to achieve full encapsulation of all four steroidal rings within the lipophilic cavity. The most important contributions to complexation thermodynamics of CDs are believed to originate from: 1) penetration of the hydrophobic part of the guest molecule into the CD cavity and 2) dehydration of the organic guest,<sup>[12]</sup> that is, the principle factors involved in the binding of CDs with organic guests are van der Waals and hydrophobic interactions. The van der Waals interactions are highly dependent on the size and shape complementarity between the guest and the CD

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[\*\*] The discovery of Org25969 is the result of teamwork with contributions from a number of scientists both inside Organon and outside the company. We would like in particular to acknowledge the following scientists for their invaluable contributions: E. Hutchinson, D. Stevenson, R. Roy, and J. Pick for scaling-up the synthesis; F. Hope, S. Miller, and R. Mason for various in vitro and in vivo pharmacological testing; R. Watson, B. Montgomery, P. Desmond, and A. Osprey for all their analytical effort; and R. McGuire and J. Mestres for graphical presentation of the X-ray crystal structure of the Org25969–rocuronium complex (Figure 3). We would also like to thank Prof. A. Cooper of Glasgow University who has critically reproduced our calorimetry data of Org25969–rocuronium complexation (Figure 2).

Table 1. In vitro reversal activity of the studied cyclodextrins against rocuronium-induced neuromuscular block in mouse hemidiaphragm.<sup>[10]</sup>

| Compound               | No. of glucose units in the ring (at conc. [ $\mu\text{M}$ ]) | Cavity dimension of the cyclodextrin |                              | $\text{EC}_{50}$ [ $\mu\text{M}$ ] <sup>[a]</sup><br>mean $\pm$ standard error | Max reversal [%] <sup>[b]</sup><br>mean $\pm$ standard error |
|------------------------|---------------------------------------------------------------|--------------------------------------|------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------|
|                        |                                                               | diameter [ $\text{\AA}$ ]            | height [ $\text{\AA}$ ]      |                                                                                |                                                              |
| $\alpha$ -cyclodextrin | 6                                                             | 4.7–5.3 <sup>[c]</sup>               | 7.9 $\pm$ 0.1 <sup>[c]</sup> | > 360.0                                                                        | 9.7 $\pm$ 3.0 (360.0)                                        |
| $\beta$ -cyclodextrin  | 7                                                             | 6.0–6.5 <sup>[c]</sup>               | 7.9 $\pm$ 0.1 <sup>[c]</sup> | > 360.0                                                                        | 29.0 $\pm$ 15.4 (360.0)                                      |
| $\gamma$ -cyclodextrin | 8                                                             | 7.5–8.3 <sup>[c]</sup>               | 7.9 $\pm$ 0.1 <sup>[c]</sup> | 34.6 $\pm$ 10.4                                                                | 94.1 $\pm$ 2.0 (144.0)                                       |
| Org 25969              | 8                                                             | <sup>[d]</sup>                       | ca. 11 <sup>[d]</sup>        | 1.2 $\pm$ 0.8                                                                  | 95.1 $\pm$ 2.3 (3.6)                                         |
| neostigmine            | –                                                             | –                                    | –                            | 0.9 $\pm$ 0.1                                                                  | 74.4 $\pm$ 9.5 <sup>[e]</sup>                                |

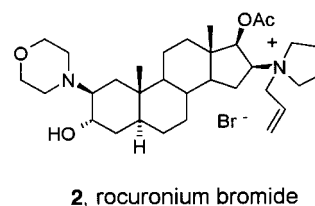
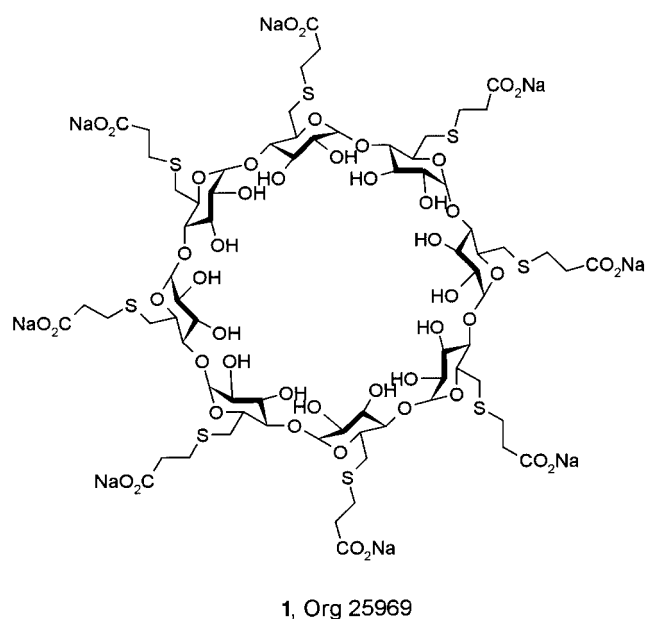
[a] Concentration that produces 50 % recovery of muscle twitch compared with prereversal twitch height. Data are presented as mean  $\pm$  standard error of four independent determinations. [b] Maximum twitch recovery achieved with highest concentration tested. Data are percentage of the prereversal twitch height ( $n = 4$ ). [c] Literature data<sup>[7]</sup> for free and uncomplexed CDs. [d] The cavity depth is estimated from the X-ray crystal structure of the Org 25969–rocuronium complex. Since the modified CD ring is somewhat puckered and some of the propionic acid side chains have been modeled as being disordered over two sites, the precise diameter of the extended cavity cannot be given. [e] Cumulative administration of neostigmine bromide caused variable results. In some preparations neostigmine caused complete reversal, whereas in other preparations only limited reversal occurred.

cavity (the size–fit concept). This means that to fully encapsulate rocuronium it is necessary to increase the cavity depth of  $\gamma$ -CD from 7.9  $\text{\AA}$  to about 11  $\text{\AA}$ , the approximate distance between the C-3 atom on ring A of the steroid and the C-16 atom on ring D. One way to achieve this is through perfacial substitution of all eight 6-hydroxyl groups of  $\gamma$ -CD with lipophilic groups. Such a per-6-modified  $\gamma$ -CD derivative would not only have a cavity with an increased depth but also an increased total area for hydrophobic interaction inside the cavity and, hence an improved hydrophobic interaction with rocuronium.

The second strategy was to introduce anionic functional groups, for example, carboxyls, at the rim of the cavity. These negatively charged groups would provide electrostatic interaction with the positively charged nitrogen atom of rocuronium, and also very importantly maintain the high water solubility of the resulting host molecule.

The biggest challenge in chemical modification of CDs is the presence of a large number of similarly reactive hydroxyl groups. Direct chemical modifications on natural CDs often result in heterogenous products, namely, mixtures of isomers.<sup>[8]</sup> To circumvent this, we chose a thioether as the linking unit for the construction of an extended cavity since this would allow us to use a nucleophilic substitution reaction involving a good nucleophile such as 3-sulfanylpropionic acid on the readily prepared per-6-iodo- or bromo- $\gamma$ -CD.<sup>[13]</sup> This modification strategy provided us with a number of chemically pure per-6-deoxy-per-6-sulfanyl- $\gamma$ -CD derivatives.<sup>[14, 15]</sup> Org25969 (**1**, Scheme 1) is one of these derivatives, in which the  $\gamma$ -CD cavity has been extended from the primary side by three carbon atoms through a thioether linkage.

As shown in Table 1, Org25969 has excellent in vitro reversal activity against rocuronium-induced neuromuscular block in isolated mouse hemi-diaphragm<sup>[10]</sup> with an  $\text{EC}_{50}$  value (1.2  $\pm$  0.8  $\mu\text{M}$ ) similar to that of neostigmine. In this assay, Org25969 produced almost complete reversal (95 %) of the muscle relaxant effects of rocuronium. Furthermore, the concentration of Org25969 required to achieve this effect was the same as the concentration of rocuronium (3.6  $\mu\text{M}$ ). Org25969 showed no observable effect on contractions of the isolated muscle when it was incubated with mouse hemidiaphragm without pretreatment with rocuronium. Org25969 did not cause any significant changes in the height of the electrically induced twitch response or the resting baseline



Scheme 1. Structures of the synthetic cyclodextrin Org25969 (**1**) and the steroidal neuromuscular blocker rocuronium bromide (**2**).

tension at concentrations up to 100  $\mu\text{M}$ , thus indicating its lack of intrinsic activity.

Consistent with its chelation mechanism of action, Org25969 has been found to form a very tight binding complex with rocuronium. The association constant ( $K_a$ ) of Org25969 to rocuronium as determined by isothermal titration calorimetry (ITC) is about  $10^7 \text{ M}^{-1}$  (Figure 1), with a negative  $\Delta H$  and positive  $\Delta S$  value, that is, the complexation is both enthalpy and entropy favored. Indeed, this level of binding affinity is rarely seen in small molecule host–guest interactions and has reached the range that is normally reserved for binding to biological macromolecules, for

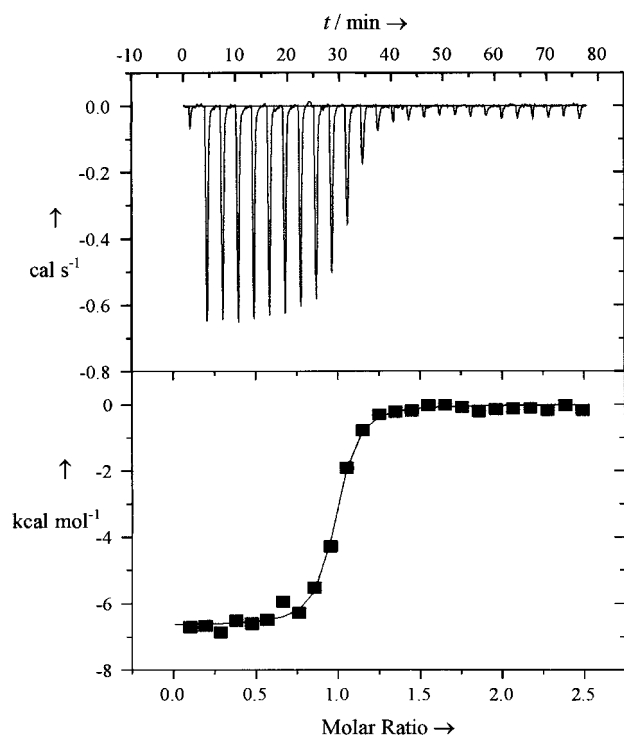


Figure 1. Isothermal calorimetry titration of Org25969 with rocuronium bromide at 25 °C. Instrument: Microcal VP-ITC (cell volume = 1.4 mL). Samples were made up by weight in 50 mM sodium phosphate buffer (pH 7.0) and degassed briefly at room temperature before loading. Standard injection sequence comprised an initial 1- $\mu$ L injection followed by  $25 \times 10$ - $\mu$ L titration injections at 3 minute intervals. A solution of Org25969 solution (21.6  $\mu$ M) was in the cell, which was titrated with rocuronium bromide solution (278.5  $\mu$ M) in the syringe. One binding site model was used to fit the data, which gives an association constant  $K_a$  of  $1.05(\pm 0.16) \times 10^7 \text{ M}^{-1}$  ( $\Delta H$ :  $-6658 \pm 60 \text{ cal mol}^{-1}$ ,  $\Delta S$ :  $9.8 \text{ cal mol}^{-1}$ ,  $N = 0.9$ ).

example, ligands to proteins. In fact, this is one of the most stable complexes of a CD with an organic guest ever reported in the literature!<sup>[12]</sup>

The structure of the Org25969–rocuronium complex has been revealed by X-ray crystallography (Figure 2). In the crystalline form, rocuronium is encapsulated inside the CD cavity, with ring A, which contains the tertiary amine, pointing towards the opening of secondary hydroxyl groups and the polar 3-OH and 2-morpholine groups protruding outside the cavity and exposed to solvent. The CD ring is somewhat puckered, with the carboxyl-containing alkyl side chains forming the walls of an extended part of the cavity. The depth of the cavity is up to 11.5 Å, as estimated from the distances between the lowest hydroxyl oxygen atom on the secondary face and the uppermost carboxyl oxygen atom in the side chains. All four steroidal rings of rocuronium are in close contact with the lipophilic area of the cavity and the quaternary ammonium group on ring D is loosely surrounded by the carboxyl groups of Org25969. No direct interaction, however, is observed between the quaternary nitrogen atom and the carboxyl groups because the quaternary nitrogen atom is sterically shielded by the alkyl substituents and most of the formal charge will have been distributed through the surrounding alkyl substituents. A presentation of the complex with full van der Waals radii showed that the two structures are highly complementary to each other and form many close contacts (Figure 2C).

We have tested Org25969 in several animal models including guinea pigs, cats, and monkeys to investigate its potential clinical use for the reversal of rocuronium-induced neuromuscular block. Figure 3 shows the *in vivo* efficacy of Org25969 in anesthetized Rhesus monkeys.<sup>[16]</sup> At 1.0  $\text{mg kg}^{-1}$  (0.5  $\mu\text{mol kg}^{-1}$ , intravenous (IV)) Org25969 reversed the rocuronium-induced block (block depth 90%) in a rapid and efficacious fashion to produce 90% recovery of muscle contraction within three minutes. By contrast, the standard treatment with neostigmine (40  $\mu\text{g kg}^{-1}$ ) and atropine (15  $\mu\text{g kg}^{-1}$ ) only produced the same level of recovery in more than six minutes. The action of Org25969 is therefore more than twice as fast as the standard treatment. Moreover,

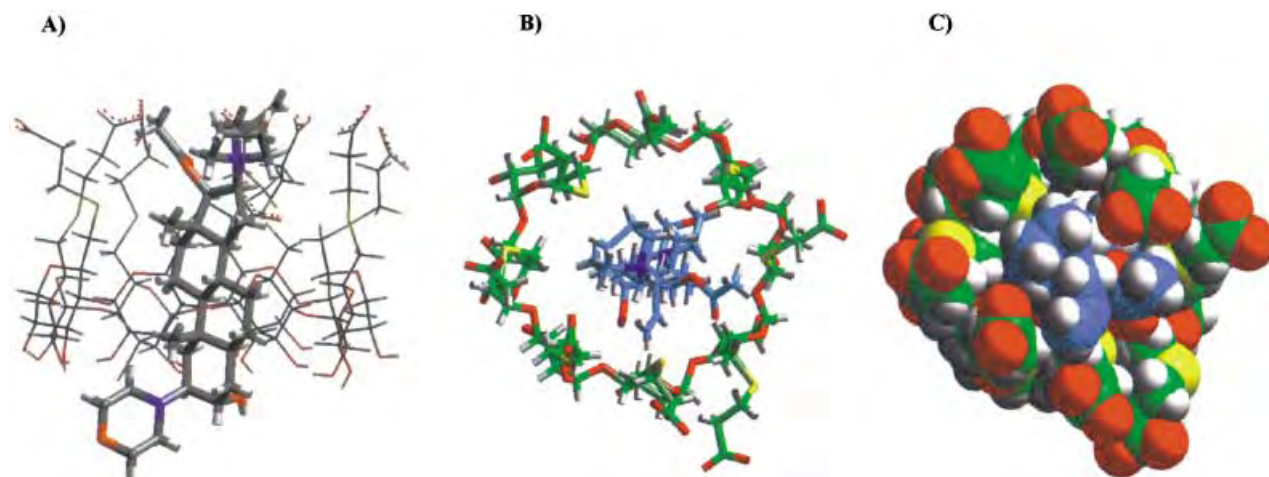


Figure 2. X-ray crystal structure of the Org25969–rocuronium complex. A) Side view showing polar substituents on ring A protruding outside the cavity from the opening of the secondary OH side and exposed to solvents. All four steroidal rings are encapsulated within the lipophilic cavity extended by per-6-alkyl substitution. B) Top-down view from the carboxyl side showing that the CD ring is somewhat puckered, with the carboxyl-containing alkyl side chains loosely surrounding the acetate and quaternary ammonium group on ring D. No direct interaction is observed between the quaternary nitrogen atom and the carboxyl groups. C) Same view as (B) but with a filled van der Waals surface showing that the two structures have many close contacts and are highly complementary to each other.



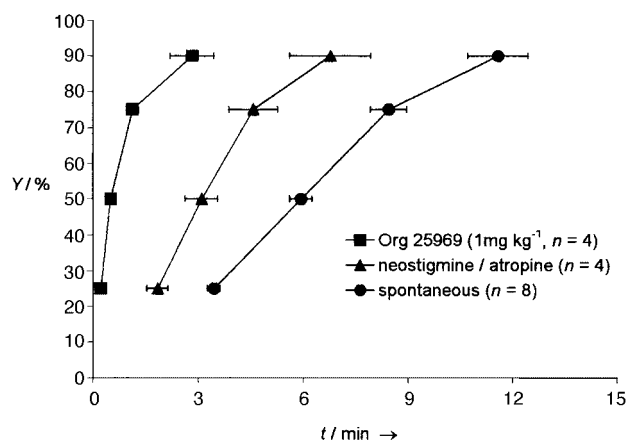


Figure 3. Reversal of rocuronium-induced neuromuscular block in anaesthetized monkeys by Org25969.<sup>[16]</sup> Ulnar nerve stimulation of anaesthetized Rhesus monkeys resulted in *M. adductor pollicis* contractions. A steady state 90% block of contractions was induced for 15–20 min by intravenous infusion of rocuronium. The infusion was then stopped to allow spontaneous recovery of muscle contractions. After complete recovery, a steady state 90% block was induced again. The infusion of rocuronium was stopped again and the reversal agent was given. The recovery of muscle contractions was measured again and the times of 25, 50, 75, and 90% recovery (*Y*) were determined. The results obtained with Org25969 (1.0 mg kg<sup>-1</sup>) and neostigmine/atropine (40/15 µg kg<sup>-1</sup>) are shown here as mean ± standard errors.

no significant changes in hemodynamic parameters, for example, blood pressure, heart rate, were observed during and after the treatment with Org25969 up to 10 mg kg<sup>-1</sup>, IV (10 times the effective dose). All animals recovered completely without any complications. The compound is currently under development in human clinical trials.

In summary, we have designed a cyclodextrin-based synthetic receptor of rocuronium bromide with high affinity as shown by ITC and X-ray crystallography data. This synthetic cyclodextrin, Org25969, reverses the NMB effect of rocuronium bromide in vitro (mouse hemi-diaphragm) and in vivo (anaesthetized monkeys). We believe that the reversal of this biological activity is mediated by chemical encapsulation of the blocker, which is a novel therapeutic approach. This cyclodextrin derivative (Org25969) and its supramolecular mechanism of action appear to be superior to currently clinically used reversal agents in terms of speed and side effects. This approach appears to be a particularly good example of using a small synthetic host molecule as a reversal agent (or antidote, antagonist) to a biologically active drug.

### Experimental Section

Org25969:<sup>[14]</sup> 3-sulfanylpropionic acid (1.22 mL, 14.0 mmol) was dissolved in dry DMF (45 mL) under N<sub>2</sub> at room temperature. Sodium hydride (1.23 g, 30.8 mmol, 60%) was added to this solution in three portions and the mixture was stirred for a further 30 min. A solution of 6-per-deoxy-6-per-iodo-γ-cyclodextrin<sup>[13]</sup> (3.12 g, 1.40 mmol) in dry DMF (45 mL) was then added dropwise to this mixture. After addition, the reaction mixture was heated at 70 °C for 12 h. After cooling, water (10 mL) was added to the mixture and the volume was reduced to 40 mL in vacuo. Addition of ethanol (250 mL) resulted in precipitation. The solid precipitate was collected by filtration and dialyzed for 36 h. The volume was then reduced to 20 mL in vacuo. Ethanol was then added, and the precipitate was collected by filtration and dried to afford Org25969 as a white solid (1.3 g, 43%). <sup>1</sup>H NMR (400.13 MHz, D<sub>2</sub>O with sodium 3-trimethylsilyl propio-

nate as reference): δ = 2.43–2.58 (m, 16H), 2.88 (t, 16H), 3.01 (dd, 8H), 3.15 (d, 8H), 3.61–3.73 (m, 16H), 3.97 (t, 8H), 4.07 (m, 8H), 5.19 (d, 8H); MS (flow injection analysis, negative ion), run as the acid: *m/z*: 2000.5 [*M* – 8Na + 7H]<sup>-</sup>.

X-Ray crystallography of the Org25969–rocuronium complex: An equimolar mixture of Org25969 (726 mg) and rocuronium (203 mg) was suspended in a DMF/H<sub>2</sub>O mixture (2.5/1, 20 mL) and heated to about 90 °C. Water was added dropwise till complete solution was achieved and a further three drops were added. The solution was allowed to cool to room temperature slowly, to afford the complex as small prisms which were recrystallized once by the same procedure. The crystal (0.30 × 0.08 × 0.02 mm) was mounted on the end of a two-stage glass fibre with perfluoropolyether oil, and cooled by a Cryostream nitrogen-gas stream.<sup>[17]</sup> The wavelength was calibrated by measurement of the unit cell parameters of a standard crystal of known structure. Single-crystal data (65420 reflections) were collected on a Bruker AXS SMART CCD area-detector diffractometer on station 9.8 at the Daresbury Laboratory.<sup>[18]</sup> The unit cell determined at 150 K is *a* = 30.9459(21), *b* = 39.2446(27), *c* = 13.3952(9) Å, α = 90°, β = 90°, γ = 90°, space group *P*<sub>2</sub><sub>1</sub>2<sub>1</sub>2, ρ<sub>calcd</sub> = 1.106 g cm<sup>-3</sup>, final *R* indices: *R*<sub>1</sub> = 0.1037, *wR*<sub>2</sub> = 0.2720. The structure was solved using the SnB program<sup>[19]</sup> which implements Shake and Bake methods (more commonly applied to protein crystallography) and refined by least-squares refinement on all unique measured *F*<sup>2</sup> values.<sup>[20]</sup> 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-172247. 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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- [10] The hemi-diaphragm with its phrenic nerve from male mice (20–30 g) was mounted on a tissue holder in a 20-mL tissue bath filled with a modified Krebs–Henseleit buffer (pH 7.4) at 37 °C, bubbled with 95% oxygen and 5% carbon dioxide. The buffer contains the following composition: NaCl: 118, KCl: 5, KH<sub>2</sub>PO<sub>4</sub>: 1, MgSO<sub>4</sub>: 1, NaHCO<sub>3</sub>: 30, CaCl<sub>2</sub>: 2.5, and glucose: 20 mM. The phrenic nerve was stimulated continuously using a Grass S88E stimulator (rectangular pulses of 0.2 ms every 20 s at a supra-maximal voltage of 2.5 V) and isometric force was recorded using Grass FT03 transducers and a Grass 79D recorder. After a stimulation period of at least 30 min, rocuronium bromide was added to the bath (final concentration of rocuronium 3.60 µM) to produce approximately 90% twitch block. Twenty minutes later, increasing concentrations of reversal agents were added in a cumulative fashion, at intervals of 10 min. The concentrations of compounds producing 50% and maximum recovery of twitch height were determined.
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## A Ring-in-Ring Complex\*\*

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Over the past two decades a vast array of interlocked and intertwined molecular compounds—specifically, catenanes, rotaxanes, and knots<sup>[1]</sup>—have been assembled using supramolecular assistance (templation<sup>[2]</sup>) as the key element in their synthesis<sup>[3]</sup> under either kinetic<sup>[4]</sup> or thermodynamic<sup>[5]</sup> control. Although these synthetic protocols have been implemented more recently for the construction of more intricate variants, such as oligocatenanes,<sup>[6]</sup> molecular necklaces,<sup>[7]</sup> and cyclic daisy chains<sup>[8]</sup> to name but a few, the

topological challenge of the de novo synthesis of Borromean ring compounds<sup>[9]</sup> still presents a considerable hurdle to be overcome. Our way of addressing this challenge is to employ recognition motifs to create initially stable ring-in-ring superstructures<sup>[10]</sup> which could serve as templates for subsequent catenation. Here, we report 1) the design and noncovalent synthesis of a prototype, mutually orthogonal, partially preorganized, ring-in-ring complex, together with 2) the solid-state characterization of the 1:1 complex in the context of the X-ray crystal structures of its two separate ring components, and 3) the solution-state behavior of the 1:1 complex.

Previously, we have shown<sup>[11]</sup> that bisparaphenylene[34]-crown-10 (BPP34C10) can encircle two dibenzylammonium (DBA<sup>+</sup>) ions simultaneously by locating the two NH<sub>2</sub><sup>+</sup> centers 6.9 Å apart in the polyether loops of BPP34C10 and relying upon N<sup>+</sup>–H···O hydrogen bonds to form a stable 1:2 (DBA<sup>+</sup> ⊂ BPP34C10 ⊃ DBA<sup>+</sup>) complex. Thus, it seemed not unreasonable to us that BPP34C10 might also be able to complex (Figure 1) with a suitably proportioned dicationic

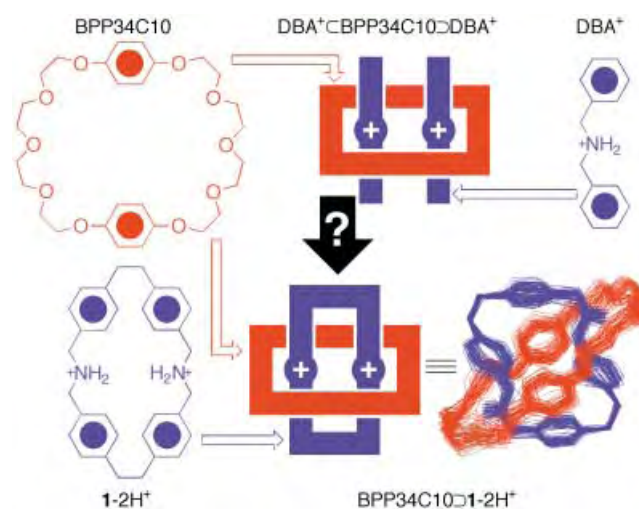


Figure 1. Employing precedent in the design and synthesis of a proposed 1:1 complex formed between BPP34C10 and 1-2H<sub>2</sub><sup>+</sup>, together with an overlaid set of 70 co-conformations of BPP34C10 · 1-2H<sub>2</sub><sup>+</sup> sampled from the last 70 ps of a 100-ps MD experiment.

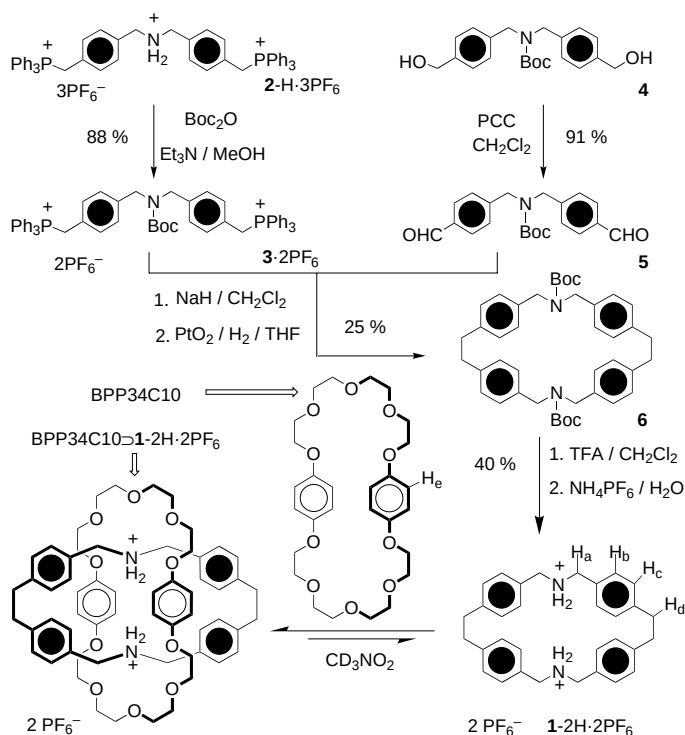
macrocycle containing two NH<sub>2</sub><sup>+</sup> centers. After inspection of the solid-state superstructure<sup>[11]</sup> of the 1:2 complex formed between BPP34C10 and DBA<sup>+</sup>, and construction of CPK space-filling molecular models, we concluded that the macrocycle 1-2H<sub>2</sub><sup>+</sup> was a suitable candidate for further investigation. Our intuition was given a considerable boost by the results of the molecular dynamics (MD) calculations.<sup>[12]</sup> They predicted the existence of a stable co-conformation<sup>[13]</sup> in which the BPP34C10 ring encircles the dicationic macrocycle, such that the polyether loops surround the NH<sub>2</sub><sup>+</sup> centers, namely, the 1:1 (BPP34C10 ⊃ 1-2H<sub>2</sub><sup>+</sup>) complex (illustrated in Figure 1) might constitute a discrete supermolecule.

The synthesis (Scheme 1) of the dicationic macrocycle 1-2H · 2PF<sub>6</sub> was achieved by employing a bis-Wittig reaction in the key cyclization step. The bisphosphonium salt<sup>[14]</sup> 2-H · 3PF<sub>6</sub> was protected (Boc<sub>2</sub>O/Et<sub>3</sub>N/MeOH) to give 3 · 2PF<sub>6</sub>

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Scheme 1. The covalent synthesis of  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  followed by the non-covalent synthesis of  $\text{BPP34C10} \supset 1\text{-}2\text{H}\cdot 2\text{PF}_6$ . Boc = *tert*-butoxycarbonyl, PCC = pyridinium chlorochromate, TFA = trifluoroacetic acid.

while the Boc-protected diol<sup>[15]</sup> **4** was converted (PCC/ $\text{CH}_2\text{Cl}_2$ ) into the appropriate dialdehyde<sup>[16]</sup> **5**. Heating of  $3\cdot 2\text{PF}_6$  with **5** in  $\text{CH}_2\text{Cl}_2$  under reflux in the presence of an excess of NaH for four days afforded the unsaturated [1+1] macrocycle as the major product following chromatography on silica gel. The macrocycle was hydrogenated immediately using a catalytic amount of Adam's catalyst in THF under an atmosphere of hydrogen to produce the di-Boc-protected macrocycle **6**. Deprotection (TFA/ $\text{CH}_2\text{Cl}_2$ ), followed by counterion exchange ( $\text{NH}_4\text{PF}_6/\text{H}_2\text{O}$ ), gave  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  as a white solid from which good quality single crystals were grown by liquid diffusion of  $i\text{Pr}_2\text{O}$  into a solution of the salt in MeCN. X-Ray crystallography<sup>[17, 18]</sup> revealed (Figure 2) that this dicationic macrocycle has a semi-open conformation possessing crystallographic  $\text{C}_{2h}$  symmetry with the two  $\text{NH}_2^+$  centers directed in toward the center of the macroring. Although the two bismethylene linkages have pseudo-*gauche* ( $46^\circ$ ) conformations, the paraxylyl ring systems are oriented so as to form the parallel-sided diamond-shaped box illustrated in Figure 2a. The separations between the two N atoms and between the centers of the two bismethylene linkages are 5.6 and 12.4 Å, respectively. The two  $\text{PF}_6^-$  counterions are located (Figure 2b) symmetrically above and below the macroring center and are held in position by a pair of  $\text{N}^+\cdots\text{H}\cdots\text{F}$  hydrogen bonds. There are no intermolecular  $\pi\cdots\pi$  stacking interactions.

The fast-atom bombardment (FAB) mass spectrum recorded on an equimolar mixture of  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  and BPP34C10 reveals a peak at  $m/z$  983 corresponding to a 1:1 complex with loss of one  $\text{HPF}_6$  and one  $\text{PF}_6^-$  ion. When equimolar amounts of the same two components (10 mm each) are dissolved in

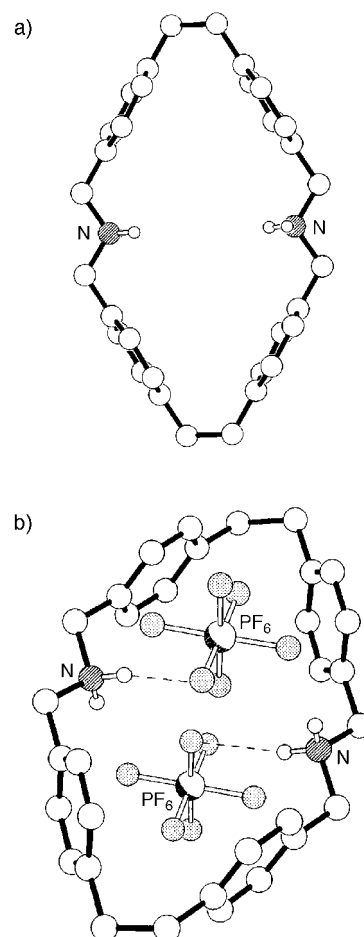


Figure 2. The solid-state structure of  $1\text{-}2\text{H}^{2+}$  viewed normal to the  $\text{C}_2$  axis and edge on to the horizontal mirror plane (a) and the solid-state superstructure of  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  showing the positioning above and below the ring center of the pair of  $\text{N}^+\cdots\text{H}\cdots\text{F}$  hydrogen-bonded  $\text{PF}_6^-$  ions (b). The  $\text{N}^+\cdots\text{F}$  and  $\text{H}\cdots\text{F}$  distances are 3.32 and 2.44 Å, respectively, and the  $\text{N}^+\cdots\text{H}\cdots\text{F}$  angle is  $169^\circ$ .

$\text{CD}_3\text{NO}_2$  at room temperature, dramatic changes in the  $^1\text{H}$  NMR spectrum are observed (Figure 3) relative to the spectra for the free host and free guest. Particularly worthy of note are the observations<sup>[19]</sup> that 1) the singlet for the hydroquinone ring protons ( $\text{H}_c$ ) of the BPP34C10 unit is shifted upfield by 0.2 ppm, 2) the signals for the  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ - $\text{OCH}_2$  protons are shifted by  $-0.1$ ,  $+0.05$ ,  $+0.10$ , and  $+0.13$  ppm, respectively, 3) one of the two “doublets” belonging to the AA’BB’ pattern of the macrocycle’s aromatic protons ( $\text{H}_b$ ,  $\text{H}_c$ ) is transformed from a sharp signal centered on  $\delta = 7.13$  into a broad one resonating at  $\delta = 6.88$ , and 4) the singlet corresponding to the methylene protons ( $\text{H}_a$ ) adjacent to the  $\text{NH}_2^+$  center at  $\delta = 4.17$  is shifted upfield by about 0.34 ppm and broadened. The considerable changes ( $\Delta\delta$ ) in the chemical shifts of the signals for the  $\text{CH}_2\text{N}^+$  protons ( $\text{H}_a$ ) and their proximal aromatic protons ( $\text{H}_b$ )—in contrast with the negligible  $\Delta\delta$  values for the bismethylene protons ( $\text{H}_d$ ) and their proximal aromatic protons ( $\text{H}_c$ )—in the macrocyclic dication upon complexation suggests that the crown ether encircles and hydrogen bonds to the  $\text{NH}_2^+$  centers such that the mean plane of the BPP34C10 ring is approximately orthogonal to that of  $1\text{-}2\text{H}^{2+}$ . Moreover, TROSEY experi-

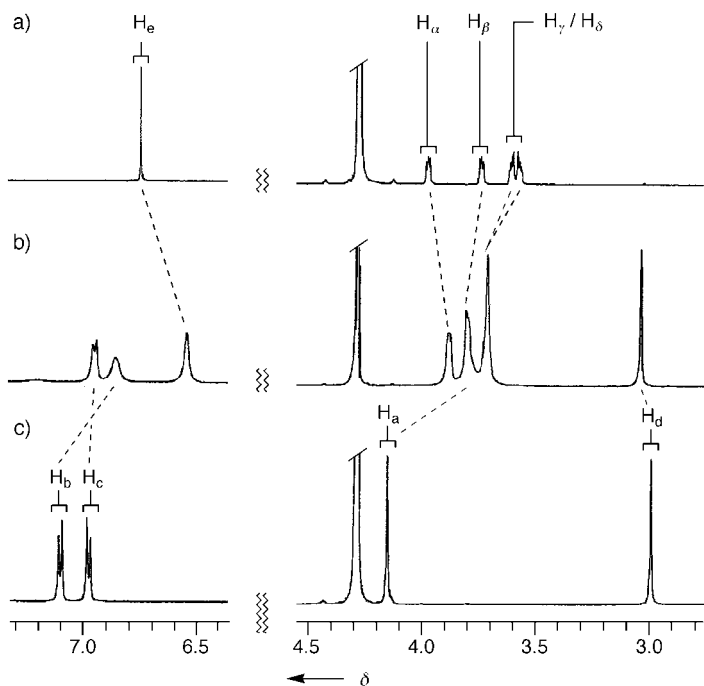


Figure 3. Partial  $^1\text{H}$  NMR spectra (500 MHz,  $\text{CD}_3\text{NO}_2$ , 298 K) of BPP34C10 (a), an equimolar mixture (10 mM) of BPP34C10 and  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  (b), and  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  (c). See Scheme 1 for the labeling of the protons.

ments,<sup>[20]</sup> using the equimolar (10 mM) mixture of  $1\text{-}2\text{H}^{2+}$  and BPP34C10 in  $\text{CD}_3\text{NO}_2$  at 298 K, show (Figure 4) cross-peaks between the signals for the hydroquinone ring protons ( $\text{H}_e$ ) in the crown ether and both the  $\text{CH}_2\text{N}^+$  protons ( $\text{H}_a$ ) and the aromatic protons ( $\text{H}_b$ ,  $\text{H}_c$ ) in the macrocyclic dication. These experimental observations were supported by the results of a further MD study in which the relative intercomponent

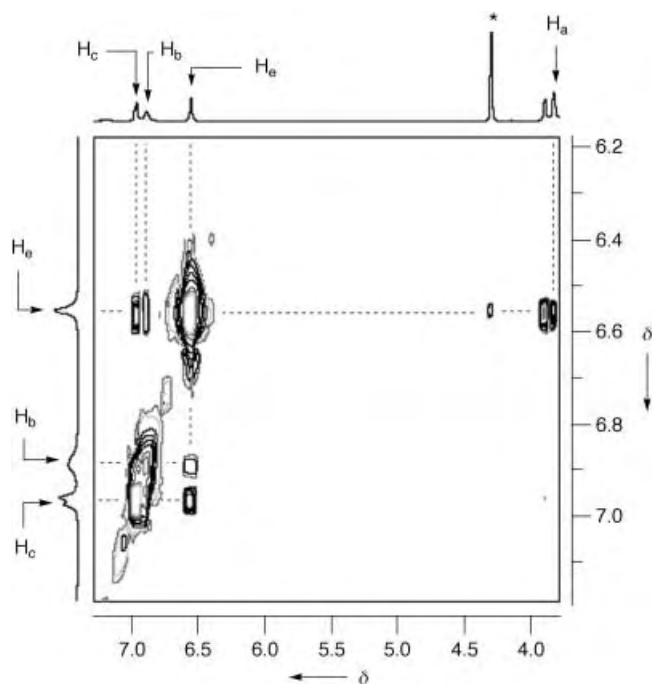


Figure 4. Partial T-ROSEY NMR spectrum (500 MHz,  $\text{CD}_3\text{NO}_2$ , 298 K) of an equimolar mixture (10 mM) of BPP34C10 and  $1\text{-}2\text{H}\cdot 2\text{PF}_6$ .

$\text{H}\cdots\text{H}$  distances were scrutinized over the course of a 1-ns MD experiment.<sup>[12]</sup> In all cases, each of the eight  $\text{H}_e$  atoms on the two hydroquinone rings of the BPP34C10 component had their distances measured to their closest corresponding  $\text{H}_a$ ,  $\text{H}_b$ , and  $\text{H}_c$  atoms in the  $1\text{-}2\text{H}^{2+}$  component. The mean interatomic distances for each pair of H atoms were then averaged in co-conformational space to give<sup>[21]</sup> 4.9, 3.3, and 3.4 Å for  $\text{H}_e\cdots\text{H}_a$ ,  $\text{H}_e\cdots\text{H}_b$ , and  $\text{H}_e\cdots\text{H}_c$ , respectively.

By using the method<sup>[22]</sup> of continuous variations (Job plot) with both the  $\text{H}_b$  atom in  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  and the  $\text{H}_e$  atom in BPP34C10 as  $^1\text{H}$  NMR probes in a mixed solvent of  $\text{CD}_3\text{CN}$  and  $\text{CD}_2\text{Cl}_2$  (1:1),<sup>[23]</sup> convincing evidence for 1:1 stoichiometry in the complexation of  $1\text{-}2\text{H}^{2+}$  by BPP34C10 was observed.  $K_a$  values in  $\text{CD}_3\text{NO}_2$  for the 1:1 complex were found to be  $4000 \pm 900$  and  $3100 \pm 500 \text{ M}^{-1}$ , using these two protons ( $\text{H}_b$  and  $\text{H}_e$ , respectively) in  $^1\text{H}$  NMR dilution experiments.<sup>[22]</sup>

Single crystals of the 1:1 complex, suitable for X-ray analysis,<sup>[18, 24]</sup> were grown by vapor diffusion of  $i\text{Pr}_2\text{O}$  into an equimolar solution of  $1\text{-}2\text{H}\cdot 2\text{PF}_6$  and BPP34C10 in a solution mixture of MeCN, MeNO<sub>2</sub>, and  $\text{CH}_2\text{Cl}_2$ . The solid-state superstructure of  $\text{BPP34C10} \supset 1\text{-}2\text{H}\cdot 2\text{PF}_6$  shows (Figure 5) the dicationic guest to be threaded, as anticipated, through the center of the crown ether host. The complex has crystallographic  $C_i$  symmetry and the BPP34C10 component has a conformation remarkably similar to that already reported<sup>[11]</sup> for the  $\text{DBA}\cdot\text{PF}_6 \subset \text{BPP34C10} \supset \text{DBA}\cdot\text{PF}_6$  complex (Figure 1), though with an increased separation between its two hydroquinone rings of 7.68 Å (centroid–centroid) compared with 6.99 Å in the 2:1 complex. The guest dication is seen to have undergone a significant change in conformation (relative to that for the free dication depicted in Figure 2), with its two  $\text{NH}_2^+$  centers now directed outwards and away from the macrocyclic center so that they can form strong  $\text{N}^+\text{H}\cdots\text{O}$  hydrogen bonds to the central oxygen atoms in the two polyether loops of the BPP34C10 host. The two bismethylene linkages still retain a pseudo-*gauche* geometry but the paraxyl ring systems are each tilted in toward their macrocyclic center. The separations between the two N atoms and the centers of the bismethylene bridges are now 7.9 and 11.1 Å, respectively. The [1+1] supermolecules form continuous stacks through  $\pi$ – $\pi$  stacking of the exterior benzenoid rings in the macrocyclic dication.

Herein we have shown that the recognition motif involving  $\text{NH}_2^+$  centers and polyether loops<sup>[11]</sup> can be employed in the noncovalent assembly of a ring-in-ring superstructure that exists, not only in the solid state, but also in solution. The control over the superstructure achieved with this particular recognition motif<sup>[25]</sup> bodes well for the covalent syntheses of Borromean ring compounds by supramolecular assistance under kinetic control.

## Experimental Section

$3\cdot 2\text{PF}_6$ :  $\text{Et}_3\text{N}$  (2.2 mL, 1.6 mmol) was added slowly by syringe over 30 min to a solution of the bisphosphonium salt<sup>[14]</sup>  $2\text{-H}\cdot 3\text{PF}_6$  (1.0 g, 0.8 mmol) and  $\text{Boc}_2\text{O}$  (3.48 g, 1.6 mmol) in MeOH (50 mL), and the reaction mixture was stirred at room temperature for 12 h. After removal of the solvent, the residue was dissolved in MeCN (10 mL) and a solution of  $\text{NH}_4\text{PF}_6$  (2 g) in  $\text{H}_2\text{O}$  (20 mL) was added. Most of the MeCN was evaporated off under reduced pressure before the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ .



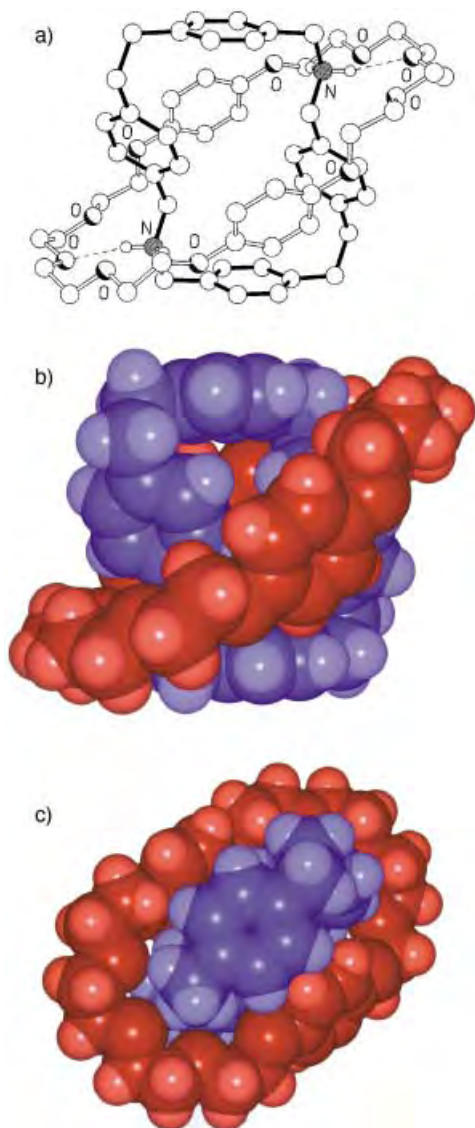


Figure 5. The ball-and-stick representation (a) of the ring-in-ring superstructure formed between BPP34C10 and  $1\text{-}2\text{H}^+$ . The  $\text{N}^+\cdots\text{H}\cdots\text{O}$  hydrogen bond has  $\text{N}^+\cdots\text{O}$  and  $\text{H}\cdots\text{O}$  distances of 2.91 and 2.04 Å, respectively, and a  $\text{N}^+\cdots\text{H}\cdots\text{O}$  angle of  $161^\circ$ . Elevation (b) and plan space-filling (c) representations of the 1:1 complex.

( $2 \times 50$  mL). The combined  $\text{CH}_2\text{Cl}_2$  extracts were dried ( $\text{MgSO}_4$ ), concentrated, and the residue was purified by column chromatography ( $\text{SiO}_2$ ;  $\text{MeCN}:\text{CH}_2\text{Cl}_2$  (3:17)) to yield  $3\cdot 2\text{PF}_6$  as a white solid (0.8 g, 88%);  $^1\text{H}$  NMR (360 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  = 1.42 (s, 9H), 4.20–4.40 (brs, 4H), 4.46 (d,  $J_{\text{PH}}$  = 14 Hz, 4H), 6.75–6.78 (m, 4H), 6.94 (brs, 4H), 7.45–7.51 (m, 12H), 7.63–7.69 (m, 12H), 7.83–7.87 (m, 6H);  $^{13}\text{C}$  NMR (90 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  = 28.7, 31.0 (d,  $J_{\text{PC}}$  = 48.6 Hz), 50.1, 80.8, 117.5 (d,  $J_{\text{PC}}$  = 85.6 Hz), 125.6, 129.1, 131.0 (d,  $J_{\text{PC}}$  = 12.5 Hz), 131.5 (d,  $J_{\text{PC}}$  = 5.4 Hz), 134.5 (d,  $J_{\text{PC}}$  = 9.6 Hz), 136.1, 139.9, 156.2; MS (FAB):  $m/z$ : 992  $[\text{M} - \text{PF}_6]^+$ , 846  $[\text{M} - \text{H} - 2\text{PF}_6]^+$ .

$1\text{-}2\text{H} \cdot 2\text{PF}_6$ :  $\text{CH}_2\text{Cl}_2$  (500 mL) was added to a round-bottom flask charged with  $3\cdot 2\text{PF}_6$  (1.35 g, 1.19 mmol) and NaH (150 mg, 6.3 mmol). The dialdehyde<sup>[15]</sup> **5** (42 mg, 1.19 mmol), dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL), was added slowly by syringe over 12 h to the reaction flask and the mixture was heated under reflux for 4 days before the reaction was quenched by the slow addition of MeOH (10 mL) and the mixture concentrated to afford a residue. Chromatographic purification ( $\text{SiO}_2$ ;  $\text{MeCN}:\text{CH}_2\text{Cl}_2$  (3:97)) removed the  $\text{Ph}_3\text{PO}$  and afforded the crude bis-Wittig product which was dissolved in THF (10 mL).  $\text{PtO}_2$  (50 mg) was added and  $\text{H}_2$  gas was bubbled through the solution for 10 min. The mixture was then stirred under  $\text{H}_2$  (balloon) for 3 h, before being concentrated to give a residue that was

subjected to column chromatography ( $\text{SiO}_2$ ; hexane: $\text{CH}_2\text{Cl}_2$ :EtOAc (16:3:1)) to yield **6** as a white solid (380 mg, 25%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.53 (s, 18H), 2.83 (s, 8H), 4.20–4.40 (brs, 8H), 6.65 (d,  $J$  = 7 Hz, 8H), 6.70–6.90 (brs, 8H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.5, 38.1, 48.3, 80.0, 127.6, 127.9, 129.5, 134.6, 139.5, 156.2; MS (FAB):  $m/z$ : 1293.6  $[\text{M} + \text{H}]^+$ . This Boc-protected diamine (100 mg, 0.08 mmol) was dissolved in a mixture of TFA (0.75 mL) and  $\text{CH}_2\text{Cl}_2$  (0.75 mL) and stirred at room temperature for 12 h. A solution of  $\text{NH}_4\text{PF}_6$  (300 mg) in  $\text{H}_2\text{O}$  (3 mL) was added to the reaction mixture. On removal of the volatile solvents, a white precipitate was formed which was filtered off and dissolved in MeCN (2 mL). Following an identical repeat treatment with aqueous  $\text{NH}_4\text{PF}_6$  solution, a white precipitate was isolated and washed with  $\text{Et}_2\text{O}$  (5 mL) to yield  $1\text{-}2\text{H} \cdot 2\text{PF}_6$  as a white solid (57 mg, 40%);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{NO}_2$ ):  $\delta$  = 3.05 (s, 8H), 4.17 (s, 8H), 7.00 (d,  $J$  = 8 Hz, 8H), 7.13 (d,  $J$  = 8 Hz, 8H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_3\text{NO}_2$ ):  $\delta$  = 37.5, 51.8, 128.5, 130.9, 131.6, 144.7; electrospray MS:  $m/z$ : 593.4  $[\text{M} - \text{PF}_6]^+$ , 447.3  $[\text{M} - \text{H} - 2\text{PF}_6]^+$ .

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## A Cucurbituril-Based Gyroscane: A New Supramolecular Form\*\*

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Cucurbit[*n*]uril, here abbreviated as *Q<sub>n</sub>* (Figure 1), are macrocyclic acid-catalyzed condensation products of glycoluril and formaldehyde.<sup>[1–6]</sup> These macrocycles have an intrinsic

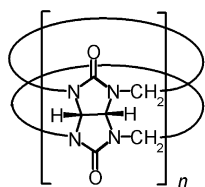


Figure 1. Schematic representation of cucurbit[*n*]uril.

capacity to act as molecular hosts. Research on the most common cucurbituril, Q6, has demonstrated the binding of guests such as xenon,<sup>[7]</sup> water,<sup>[8]</sup> tetrahydrofuran,<sup>[9]</sup> toluene,<sup>[10]</sup> and pyridinium<sup>[11]</sup> and *p*-xylylene-diammonium<sup>[12]</sup> ions within the cyclic host. Many alkyl diamines thread through the Q6 cavity.<sup>[4, 12]</sup> These guests can be functionalized to provide the basis for a family of rotaxane

structures.<sup>[13]</sup> Metal complexes of tetraazamacrocycles contained within Q8,<sup>[14]</sup> and *cis*-[SnCl<sub>4</sub>(OH<sub>2</sub>)<sub>2</sub>] within Q7,<sup>[15]</sup> have been described. *o*-Carborane also binds in Q7 as a globular guest.<sup>[16]</sup>

Here we report the formation and characterization of a supramolecular form in which a smaller macrocycle, Q5, is located inside a larger macrocycle, Q10, with facile rotation of one relative to the other in solution. The image of a ring rotating independently inside another ring, which resembles a gyroscope, suggests the name gyroscane for this new class of supramolecular system.

We recognized the formation of this gyroscane while investigating the controlled synthesis of cucurbit[*n*]urils.<sup>[5]</sup> The <sup>13</sup>C NMR spectrum of each *Q<sub>n</sub>* contains three peaks: there is progressive change in the chemical shift of peaks associated with the methylene and methine carbon atoms that is dependent on *n*. Monitoring of the fractional crystallization of our crude *Q<sub>n</sub>* reaction mixture by <sup>13</sup>C NMR spectroscopy showed there to be two sets of unidentified *Q<sub>n</sub>* peaks: one set of peaks corresponded to the previously unknown Q10,

whereas the other set of peaks did not correspond to either the known Q5 resonances or those predicted for Q4.<sup>[5b]</sup> The relative intensities of these two sets remained unchanged despite repeated recrystallizations. Only these two sets of resonances finally remained in the <sup>13</sup>C NMR spectrum of the crystalline material.

Electrospray mass spectrometry of this sample gave an ion that was equivalent to a Q15 species (as the [Q15+2 Cs]<sup>2+</sup> ion, *m/z* 1378), which suggested that the unidentified <sup>13</sup>C resonances arose from Q5. The X-ray crystal structure<sup>[17]</sup> of single crystals grown in concentrated HCl unambiguously identifies this new supramolecular structure as Q5 encapsulated within Q10, namely Q5@Q10. We have isolated 65 grams of Q5@Q10 from a 1 kg scale synthesis.<sup>[5b]</sup>

The key feature of the crystalline structure of this gyroscane is the concentric location of Q5 inside Q10, with the molecular axis of Q5 inclined strongly (64°) to the axis of Q10. There is a Cl<sup>−</sup> ion at the center of Q5,<sup>[18a]</sup> and a hydrogen atom from an OH<sub>2</sub> molecule or OH<sub>3</sub><sup>+</sup> ion bound over each of the two carbonyl portals of Q5 (Figure 2) such that the inner component of the gyroscane is Cl@Q5·(OH<sub>2</sub>)<sub>2</sub> (**1**), with a Cl<sup>−</sup> ion and two water molecules coaxial with Q5.<sup>[18b]</sup> Figure 3 shows the location and orientation of **1** inside Q10. Each of the water molecules capping the Q5 portals is also well inside Q10 and near two of its carbonyl oxygen atoms, and hence has

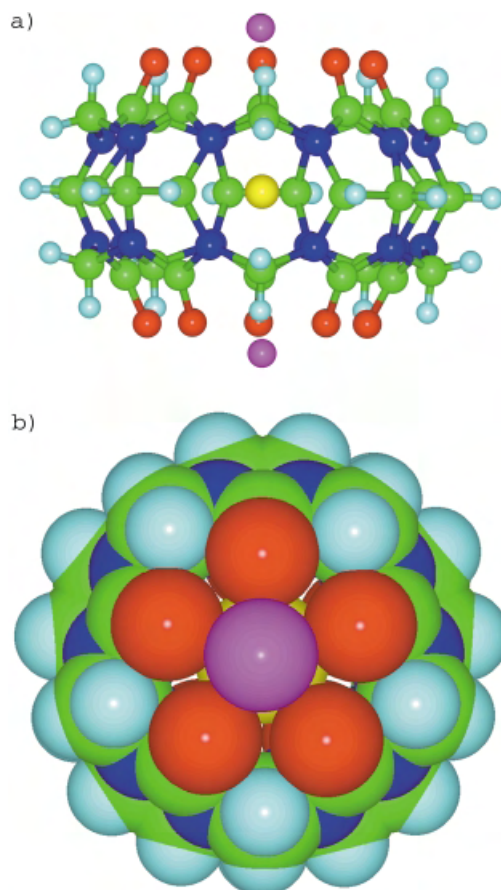


Figure 2. The inner component Cl@Q5·(OH<sub>2</sub>)<sub>2</sub> (**1**) of the gyroscane: a) side elevation (ball-and-stick representation); b) axial view of Q5 (space-filling representation). C: green, N: blue, O: red, H: cyan, Cl: yellow, O(water): magenta.

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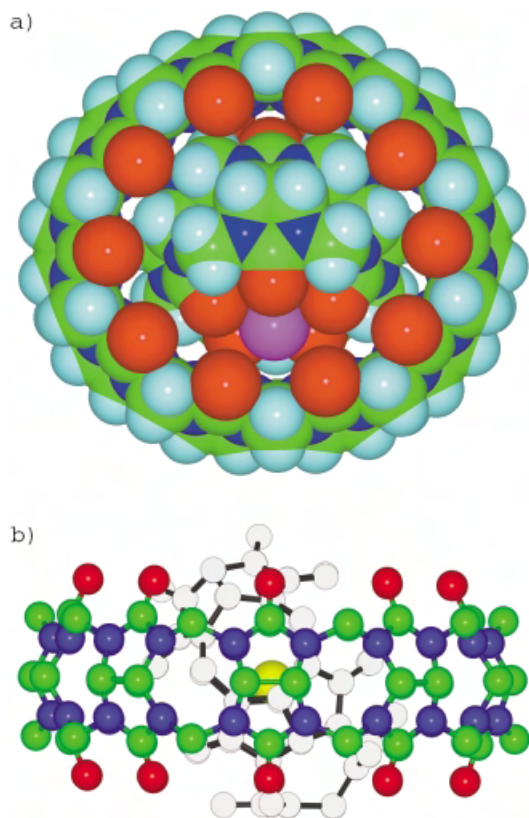


Figure 3. Inclusion of Q5 component (**1**) inside Q10: a) axial view of Q10 (space-filling representation); b) side elevation (ball-and-stick representation). The angle between the axis of the inner component and the axis of Q10 is 64°. C: green, N: blue, O: red, H: cyan, O(water): magenta.

a number of hydrogen-bonding possibilities. There is some protrusion of the inner component through the portals of the Q10 macrocycle (Figure 3b). The fivefold symmetry of Q5 means that when the axes of Q5 and Q10 are inclined, different surfaces of Q5 are exposed at the two portals of Q10: on one side a flat imidazolidinone ring is parallel to the face of the portal (revealed in Figure 3b), while at the other portal of Q10 the bismethylene linkage is exposed. The angled orientation of **1** within Q10 in the crystal is influenced by offset-face-to-face intermolecular interactions between exposed imidazolidinone faces of adjacent molecules of  $(\text{Cl}@\text{Q5} \cdot (\text{OH}_2)_2)@\text{Q10}$ . The interannular relationship between concentric cucurbituril molecules is geometrically analogous to a section of fullerene “onions”.<sup>[19]</sup>

The integrity of Q5@Q10 in solution is demonstrated by the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of this gyroscane in 18% w/v DCl/D<sub>2</sub>O. The spectra (Figure 4a) show no evidence of dissociated Q5 at concentrations down to  $2 \times 10^{-4}$  M, which indicates that the association constant for Q5@Q10 is  $>10^6$ . When Q5 is added to a solution of Q5@Q10, it appears in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra as resonances for unbound Q5 (Figure 4b, d). These spectra show that there is slow exchange between endo-annular Q5 and exo-annular Q5 on the NMR time scale. However, this exchange of Q5 does occur at room temperature within one hour, as revealed by the equilibrated  $^{13}\text{C}$  spectrum when  $^{13}\text{C}$ -labeled Q5 was added to Q5@Q10 in 18% w/v DCl/D<sub>2</sub>O. The rate of exchange could not be determined,

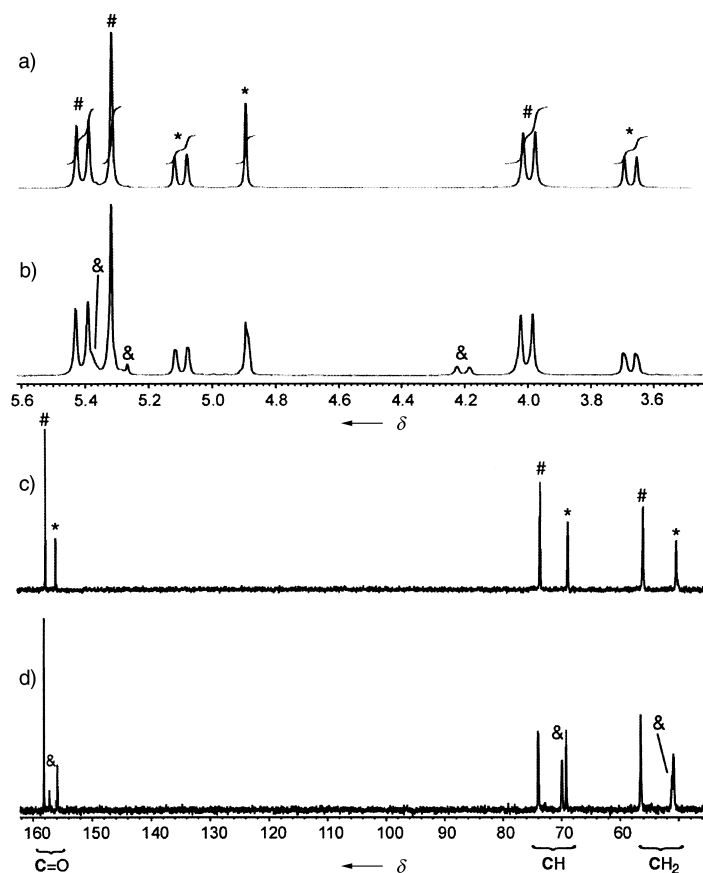


Figure 4. a)  $^1\text{H}$  NMR spectrum of Q5@Q10 in 18% w/v DCl/D<sub>2</sub>O; b)  $^1\text{H}$  NMR spectrum of Q5@Q10 with additional Q5; c)  $^{13}\text{C}$  NMR spectrum of Q5@Q10 in 18% w/v DCl/D<sub>2</sub>O; d)  $^{13}\text{C}$  NMR spectrum of Q5@Q10 with additional Q5. Note: In the  $^1\text{H}$  NMR spectra, the methylene hydrogens are nonequivalent, and give rise to the pair of doublets observed for each cucurbit[n]uril. The methine hydrogen atom is observed as a singlet in each case. #, \*, and & represent Q10, Q5 encapsulated in Q10, and unbound Q5, respectively.

as the exchange is faster than the time required to accumulate sufficient data to achieve an acceptable spectrum (see the Supporting Information).

It is our view that the significant yield of Q10,<sup>[5b]</sup> albeit associated with Q5, occurs as a consequence of the association of Q5 with Q10. One explanation is that Q5 acts as a template in the synthesis of Q10. However, this appears unlikely, since the addition of Q5 to the reaction mixture does not affect the final yield of Q10. The synthesis of cucurbit[n]urils produces only trace amounts of Q9 ( $<1\%$ ),<sup>[5b]</sup> and even lower amounts of higher homologues, apart from Q10, which suggests that the higher homologues are unstable. By contrast, Q10 appears to be stabilized by Q5. At no time has Q10 been isolated, or detected, free of Q5.

Rapid re-orientation of Q5 in Q5@Q10 is revealed by the single set of  $^1\text{H}$  and  $^{13}\text{C}$  resonances for both components, and there is no evidence of signal broadening at 2 °C. There must be, therefore, rapid gyroscopic-like motion around the principal axes of both Q5 and Q10 for dynamic averaging of *both* the host Q10 and the guest Q5 to be achieved. Q5 undergoes both axial rotation and precessive rotation in the Q10 framework.

The O...O diameters of the carbonyl portals of Q10 range from 12.07 to 14.73 Å (mean value: 13.13 Å). The maximum diameter, H...H, of Q5 is 10.6 Å (including the van der Waals radii). Q5 can pass through the Q10 portal in the inclined conformation (Figure 3b). Other conformations of Q5@Q10, such as coaxial (Figure 5), would require distortion of the Q10 cage for egress to occur. The snug fit of Q5 in Q10 is consistent with its slow egress through the portal of Q10.

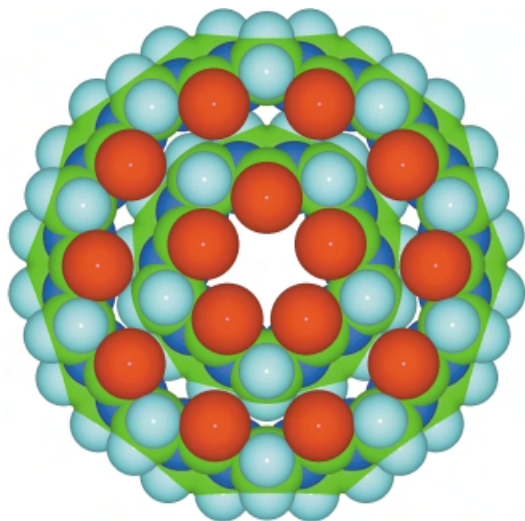


Figure 5. A probable coaxial conformation of Q5@Q10.

In summary, we have isolated and characterized the first example of a small cucurbituril contained within a large cucurbituril as a crystalline material that can be readily prepared in large amounts. The two macrocyclic rings are concentric but not coaxial in the crystal. It is evident that both rings are freely rotating relative to each other in solution. Facile axial and precessive motion of the inner ring relative to the outer ring represents the molecular analogy of the gyroscope: the gyroscane is a new potential molecular machine,<sup>[20]</sup> with analogy to carbon-nanotube linear bearings.<sup>[21]</sup>

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# Design of a Protein Surface Antagonist Based on $\alpha$ -Helix Mimicry: Inhibition of gp41 Assembly and Viral Fusion\*\*

Justin T. Ernst, Olaf Kutzki, Asim K. Debnath, Shibo Jiang, Hong Lu, and Andrew D. Hamilton\*

The design of low molecular weight ligands (<750 Da) that disrupt protein–protein interactions has remained a challenging endeavor.<sup>[1]</sup> Conventional means of identifying small molecules from chemical libraries that are inhibitors of protein–protein interactions have resulted in limited success.<sup>[2]</sup> Therefore, new strategies focusing on the rational design of molecules that recognize protein surfaces could prove fruitful in the development of novel antagonists. Herein we describe such a strategy based on the design of a molecular scaffold that mimics the surface of an  $\alpha$ -helix. We have designed a proteomimetic of an  $\alpha$ -helical 4-3 hydrophobic repeat that inhibits the assembly of a six-helix bundle corresponding to the fusion-active conformation of the gp41 protein.<sup>[3]</sup> This intraprotein surface disruption results in reduced levels of HIV-1 entry into host cells.

The gp41 ectodomain contains an N-terminal glycine-rich fusion sequence, as well as two helical regions containing hydrophobic 4–3 heptad (*abcdefg*) repeats denoted as the N- and C-helical regions (N and C refer to regions situated towards the N- and C-terminus, respectively, Figure 1). Recent evidence has shown that gp41 undergoes a conformational change upon binding target surface cell receptors which exposes the hydrophobic N-helical regions and allows the fusion peptides to insert into the host cell membrane.<sup>[4]</sup> This transient gp41 intermediate then refolds into a stabilized six-helix bundle structure, which brings both the viral and target cell membranes into proximity and results in completion of the fusion process. The fusion-critical helix bundle has been shown by X-ray diffraction data to exist as a gp41 trimer in which the N-helical regions form a parallel trimeric coiled coil and the C-helical regions subsequently pack in an antiparallel fashion into the hydrophobic grooves formed by the coiled coil (Figure 1).<sup>[3a]</sup>

Antagonists that bind the exposed N-helical regions of the transient gp41 intermediate can potentially trap this structure prior to bundle formation, which leads to inhibition of viral fusion.<sup>[3a, 5]</sup> Peptides with sequences corresponding to the

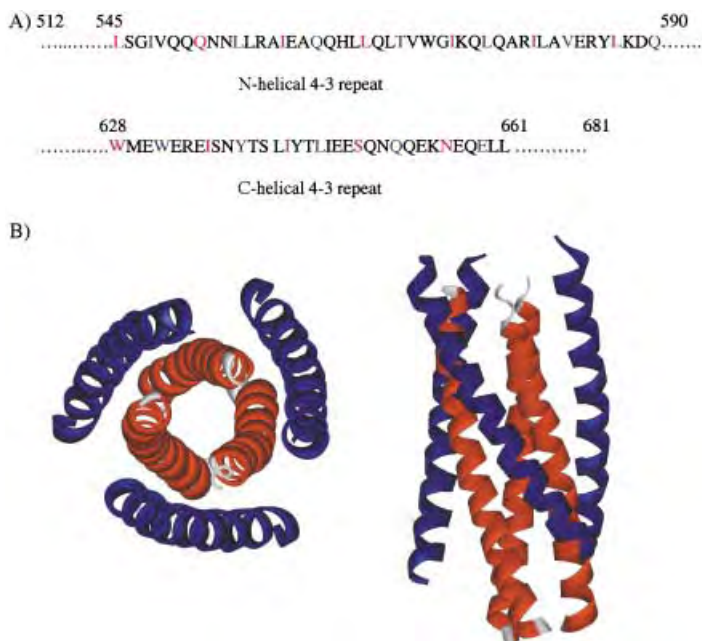


Figure 1. A) Sequences of the gp41 ectodomain corresponding to the helical 4–3 repeat regions (aa 545–590 and 628–661). The residues colored in red and blue correspond to the *a*- and *d*-positions, respectively, in the heptad repeat. B) Top and side views of the crystal structure of the fusion active core of gp41. The helices correspond to the N36 (red, aa 546–581) and the C34 peptides (blue, aa 628–661).

C-helical region of gp41 are potent inhibitors of HIV fusion,<sup>[6]</sup> one of which is currently in human trials.<sup>[7]</sup> Small molecules that bind into a hydrophobic pocket in the N-helical trimer inhibit viral fusion in vitro, with activities in the low micromolar range.<sup>[2b, 8]</sup> However, other sites along the hydrophobic grooves of the N-helical trimer are also important for recognition of the C-helical region,<sup>[3a, 9]</sup> as evidenced by the strong binding of C-terminal peptides that lack the key Trp residues ( $W_{628}$  and  $W_{631}$  in gp41).<sup>[6b, 10]</sup> Also, small peptides corresponding to the pocket binding region have negligible viral fusion inhibition and mutations of C-terminal peptide residues distant from the  $W_{628}$  and  $W_{631}$  binding region abolish inhibition activity.<sup>[11, 12]</sup> These results suggest that a small molecule mimetic of the helical 4–3 hydrophobic repeats could bind multiple sites along the coiled coil of the N-helical region, and disrupt formation of the helix bundle.

Trisubstituted 3,2',2''-terphenyl derivatives serve as effective mimics of the surface functionality projected along one face of an  $\alpha$ -helix.<sup>[13]</sup> To target the gp41 complex we prepared terphenyl derivative **1a**, which mimics the side chains of an *i*, *i* + 4, *i* + 7 *dad* hydrophobic surface, as found in the heptad repeat regions of the C- and N-peptides. Although there are a range of hydrophobic residues at the *a*- and *d*-positions (Figure 1), Leu and Ile are the most prevalent. Therefore, we have incorporated the related branched alkyl substituents isobutyl and isopropyl (to avoid complications from chirality in a *sec*-butyl group) into our initial design. Terminal carboxylate groups were also added to mimic the anionic character of the C-helical region of the peptide and to improve the aqueous solubility.

The low energy barrier of rotation about the phenyl–phenyl bonds in this system<sup>[14]</sup> makes an energetically mini-

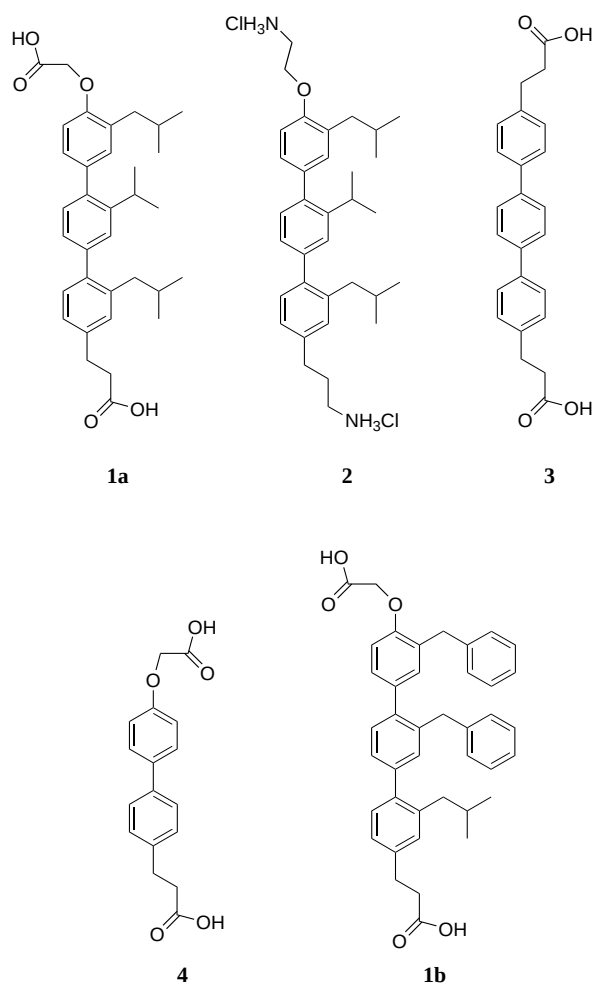
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mized conformation accessible that presents the phenyl substitution in a way that mimics the *i*, *i* + 4, and *i* + 7 side chains (Figure 2). Computer modeling experiments comparing a polyalanine  $\alpha$ -helix to 3,2',2''-trimethylterphenyl indicated that phenyl–phenyl torsion angles of  $55^\circ$  gave a

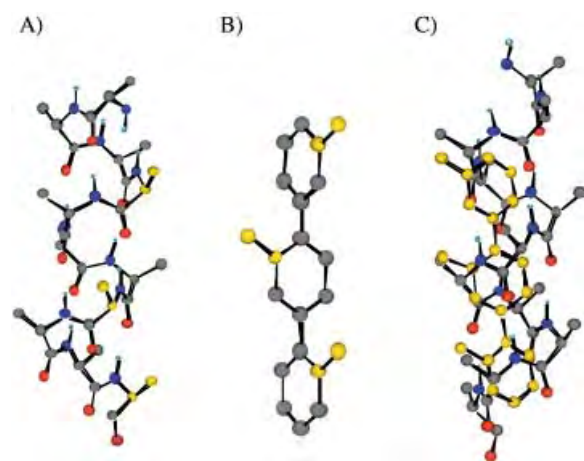
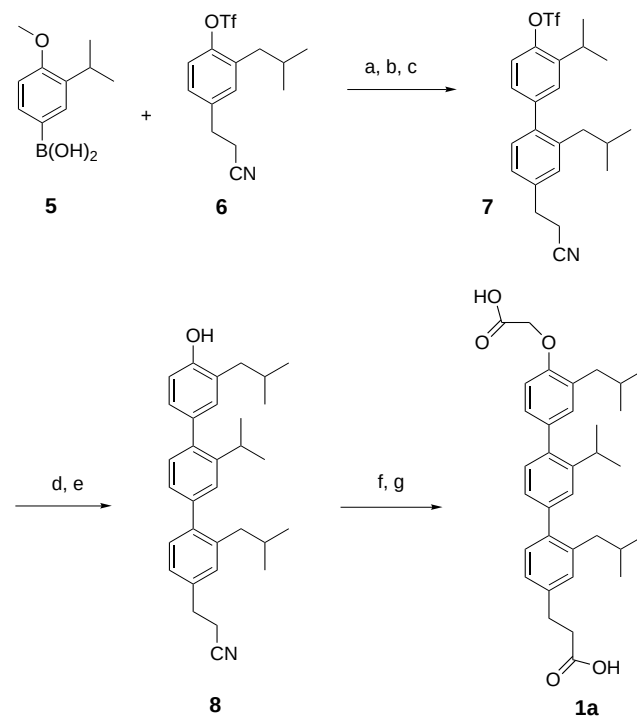


Figure 2. A) Structure of a polyalanine  $\alpha$ -helix. B) Structure of 3,2',2''-trimethyl terphenyl (hydrogen atoms omitted). The analogous carbon atoms between structures are highlighted in yellow. C) Root mean square difference overlay of a polyalanine  $\alpha$ -helix and 3,2',2''-trimethylterphenyl (yellow).

conformation with close correspondence (root mean square deviation rmsd =  $0.9 \text{ \AA}$ ) of the positions of the three methyl groups and the *i*, *i* + 4, *i* + 7 alanine methyl groups (yellow in Figure 2).<sup>[15]</sup> Facile phenyl–phenyl bond rotation should allow interconversion among the conformations necessary for an induced fit upon binding to the N-peptide trimer.

A convergent synthesis of **1a** (Scheme 1) was developed based on sequential Suzuki coupling reactions. The individual 1,4-alkoxyphenylboronate monomers could be readily prepared with different substituents at the 2-position. Compounds **2–4**, with opposite charge or lacking the branched alkyl substituents, were also synthesized as controls.



Scheme 1. a)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Na}_2\text{CO}_3$  (aq), DME/EtOH,  $80^\circ\text{C}$ , 17 h, 98%; b)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0-10^\circ\text{C}$ , 9 h, 92%; c)  $\text{Tf}_2\text{O}$ , pyridine,  $0^\circ\text{C}$ –RT, 17 h, 95%; d)  $\text{Pd}(\text{PPh}_3)_4$ , 2-(3-isobutyl-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane,  $\text{Na}_2\text{CO}_3$  (aq), DME/EtOH,  $80^\circ\text{C}$ , 20 h, 87%; e)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0-10^\circ\text{C}$ , 9 h, 97%; f)  $\text{CH}_2\text{ClCN}$ ,  $\text{K}_2\text{CO}_3$ , acetone,  $55^\circ\text{C}$ , 40 h, 95%; g)  $\text{NaOH}$  (aq), MeOH,  $50^\circ\text{C}$ , 24 h, 74%. DME = 1,2-dimethoxyethane, Tf = trifluoromethanesulfonyl.

The ability of **1a** to influence the disruption of the gp41 core was studied by CD spectroscopy. A model system composed of two peptides (N36 and C34), from the N- and C-heptad repeat regions of gp41, forms a stable six-helix bundle ( $T_m = 66^\circ\text{C}$ ) that is analogous to the gp41 core (Figure 3).<sup>[3]</sup> CD experiments show that the C34 peptide alone in solution is a random coil and the N36 peptide alone forms concentration-dependent aggregates.<sup>[3b]</sup> Titration of **1a** into a  $10 \mu\text{M}$  solution (50 mM phosphate-buffered saline (PBS), 150 mM NaCl, pH 7.0,  $4^\circ\text{C}$ ) of the preformed gp41 core model resulted in a decrease of the CD signal at  $\theta_{222}$  and 208 nm which corresponds to a reduction in the helicity of the hexameric bundle (Figure 3). A plot of  $\theta_{222}$  versus inhibitor concentration (Figure 4) shows saturation at approximately three

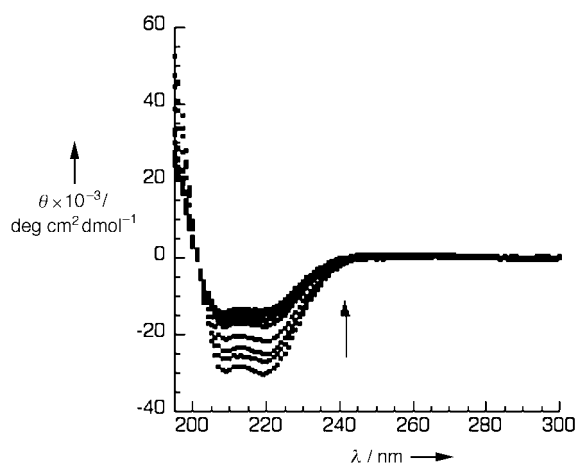


Figure 3. CD spectra of a 10  $\mu\text{M}$  solution (50 mM PBS, 150 mM NaCl, pH 7.0, 4  $^{\circ}\text{C}$ ) of the gp41 core model upon titration of **1a** (0–50  $\mu\text{M}$ ). The arrow indicates the reduction in signal at  $\theta_{222}$  and 208 nm.

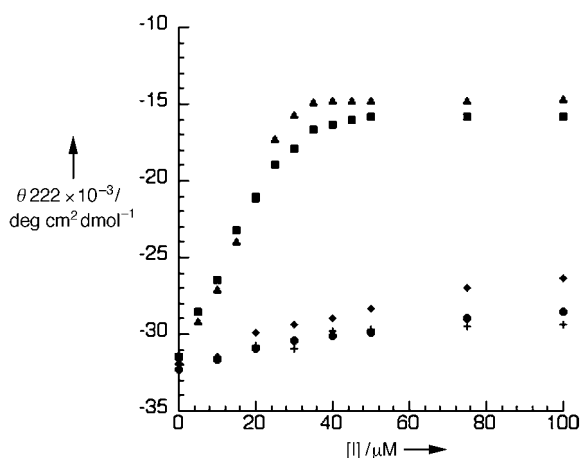


Figure 4. CD signal at  $\theta_{222}$  nm versus inhibitor concentration: **1a** (■); **2** (◆); **3** (●); **4** (+); and **1b** (▲). The inhibitors were titrated into a 10  $\mu\text{M}$  aqueous solution of the gp41 model complex (50 mM PBS, 150 mM NaCl, pH 7.0, 4  $^{\circ}\text{C}$ ).

equivalents of **1a**. The CD spectrum with excess **1a** was similar to the theoretical addition of the individual N36 and C34 spectra at the same concentration.<sup>[15]</sup> The thermal denaturation curve of the gp41 core in the presence of 50  $\mu\text{M}$  **1a** shows a significant drop in the  $T_m$  value ( $\Delta T_m = 18^{\circ}\text{C}$ ) and closely resembles the melting transition of N36 alone at the same concentration (Figure 5).<sup>[3b]</sup> These data suggest that the hexameric helix bundle structure is disrupted by helix mimetic **1a**, presumably by displacement of the C34 peptide.

Both the hydrophobic and electrostatic features of **1a** are important for its ability to disrupt the bundle. Analogues **3** and **4**, which lack the key alkyl side chains, and analogue **2**, with positively charged substituents on the hydrophobic core, have little effect on the CD spectrum of the protein even at high concentrations (Figure 4). Also, thermal denaturation experiments showed that **2–4** (at 100  $\mu\text{M}$ ) had no effect on the melting transition of the system (Table 1). To test the scope of this strategy we have increased the size of the hydrophobic substituents in **1a**, by using the bis-benzyl substituted **1b**. This molecule shows a modest enhancement in activity relative to

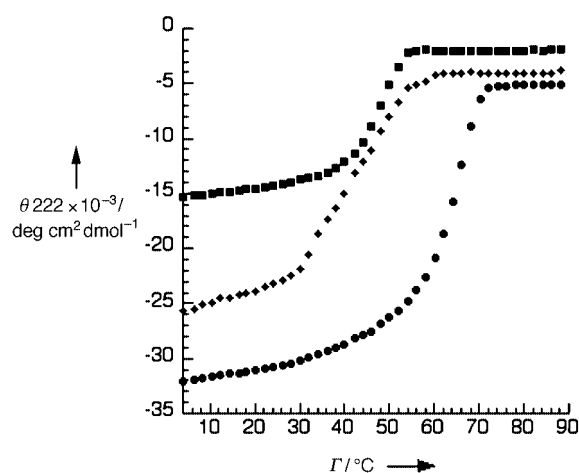


Figure 5. CD thermal denaturation experiments: 10  $\mu\text{M}$  gp41 core model (●); 10  $\mu\text{M}$  gp41 core model in the presence of 50  $\mu\text{M}$  **1a** (■); and 10  $\mu\text{M}$  N36 (◆).

Table 1. Inhibitory activities of compounds **1a–4**.  $T_m$  refers to the thermal melting transition of 10  $\mu\text{M}$  gp41 core in the presence of inhibitor: **1a** (50  $\mu\text{M}$ ), **2–4** (100  $\mu\text{M}$ ).

| Inhibitor | $T_m$<br>[ $^{\circ}\text{C}$ ] | N36/C34 ELISA $\text{IC}_{50}$<br>[ $\mu\text{g mL}^{-1}$ ] | Cell Fusion $\text{IC}_{50}$<br>[ $\mu\text{g mL}^{-1}$ ] |
|-----------|---------------------------------|-------------------------------------------------------------|-----------------------------------------------------------|
| <b>1a</b> | 48                              | $13.18 \pm 2.54$                                            | $15.70 \pm 1.30$                                          |
| <b>2</b>  | 65                              | > 100                                                       | —[a]                                                      |
| <b>3</b>  | 66                              | > 100                                                       | —[a]                                                      |
| <b>4</b>  | 66                              | > 100                                                       | —[a]                                                      |

[a] No inhibition was detected below concentrations that caused cytotoxicity ( $\sim 25$ –50  $\mu\text{g mL}^{-1}$ ).

**1a** (Figure 4), fully disrupting the hexameric bundle at a lower concentration.

The disruption of the hexameric bundle seen in the CD experiments was supported by an enzyme-linked immunosorbent assay (ELISA) for gp41 core disruption using an antibody that binds the N36/C34 helix bundle but not the individual peptides (Table 1).<sup>[16]</sup> Mimetic **1a** effectively disrupts N36/C34 complexation with an  $\text{IC}_{50}$  value of  $13.18 \pm 2.54 \mu\text{g mL}^{-1}$ , while **2–4** have no effect at 100  $\mu\text{g mL}^{-1}$ .

Finally, the effects of antagonist **1a** on HIV-1 mediated fusion were studied using a dye-transfer cell fusion assay.<sup>[17]</sup> If the gp41 core is being disrupted, as implied by the CD and ELISA experiments, then the fusion mechanism of HIV-1 should be inhibited. Indeed, **1a** shows inhibition of HIV-1 mediated cell-to-cell fusion with an  $\text{IC}_{50}$  value of  $15.70 \pm 1.30 \mu\text{g mL}^{-1}$  (Table 1). In comparison, compounds **2–4** had no inhibitory activity and proved to be cytotoxic at similar concentrations (data not shown).

In conclusion, a strategy of helix mimicry based on a substituted terphenyl scaffold was applied to the design of an antagonist of gp41 core formation. CD and ELISA experiments suggest that **1a** disrupts the formation of a six-helix bundle corresponding to the gp41 fusion-active conformation, subsequently resulting in the inhibition of HIV-1 entry into host cells. The structural and mechanistic similarities of gp41 to fusion-mediating subunits of other enveloped viral glyco-



proteins suggest that such a universal inhibitor design could potentially be effective against several different viruses.<sup>[18]</sup>

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## A Breathing Hybrid Organic–Inorganic Solid with Very Large Pores and High Magnetic Characteristics

Karin Barthelet, Jérôme Marrot, Didier Riou,\* and Gérard Férey

Porous solids<sup>[1]</sup> usually find applications in the areas of ion-exchange, separation, and catalysis. The recent discovery of new materials based upon transition metal ions<sup>[2]</sup> opens the possibility of making open frameworks that exhibit also some of the remarkable electronic properties of condensed transition metal compounds (ferro- and ferrimagnetism, metal-semiconductor transitions, ferroelectricity, combined ionic/electrical conductivity). Up to now, in the field of magnetism, the major limitation for producing porous solids with high ordering temperatures came from the structure itself. Indeed, most of the porous compounds are built from metallic clusters linked by diamagnetic linkers (phosphates, arsenates, silicates, aliphatic chains) which prevent strong, long-range interactions. To date, the highest Néel temperatures were observed for the purely inorganic porous skeleton of ULM-3<sup>[3]</sup> (37 K) and for the hybrid solid HKUST-1<sup>[4]</sup> (75 K).

To overcome this difficulty, our design strategy is to link chains of corner-sharing transition metal octahedra (which favor strong, long-range superexchange coupling) by rigid organic linkers containing delocalized  $\pi$  electrons for the three-dimensional transmission of the interactions. The use of such linkers was mainly developed by the groups of Yaghi and O'Keeffe,<sup>[5a]</sup> Zaworotko,<sup>[5b]</sup> and Kitagawa<sup>[5c]</sup> for metal-organic frameworks with modulable very large pores.

As an example of our design principle, we describe here the synthesis, structure, magnetic and sorption properties of a large-pore, flexible, open framework (MIL-47) that is antiferromagnetic below 95 K.

To implement this design, we used the hydrothermal reaction (teflon-lined steel autoclave Parr, four days, 473 K, autogenous pressure, filling rate: 50 %) of either a mixture of  $\text{VCl}_3$ , terephthalic acid, and desionized water (molar ratio 1:0.25:100), which only provides homogeneous pure powders, or of vanadium metal, terephthalic acid, hydrofluorhydric acid, and water (molar ratio 1:0.25:2:250) when crystals are needed. In both cases, the pH value remains 1 throughout the synthesis and the yield is close to 15 %. The resulting light yellow product, (hereafter labeled MIL-47as), which is stable in air, is formulated  $\text{V}^{\text{III}}(\text{OH})\{\text{O}_2\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\} \cdot x(\text{HO}_2\text{C}-\text{C}_6\text{H}_4-\text{CO}_2\text{H})$  ( $x \sim 0.75$ ) on the basis of elemental analysis (calcd: C 47.1, V 14.3; found: C 46.87, V 13.79;). Both thermogravimetry and thermal analyses (TGA2050 TA apparatus,  $\text{O}_2$  flow, heating rate  $2 \text{ K min}^{-1}$ ) show (Figure 1a) a decomposition of MIL-47as in two steps between 300 and  $420^\circ\text{C}$ . The first weight loss (exp.: 32.3 %, calcd: 34.92 % for

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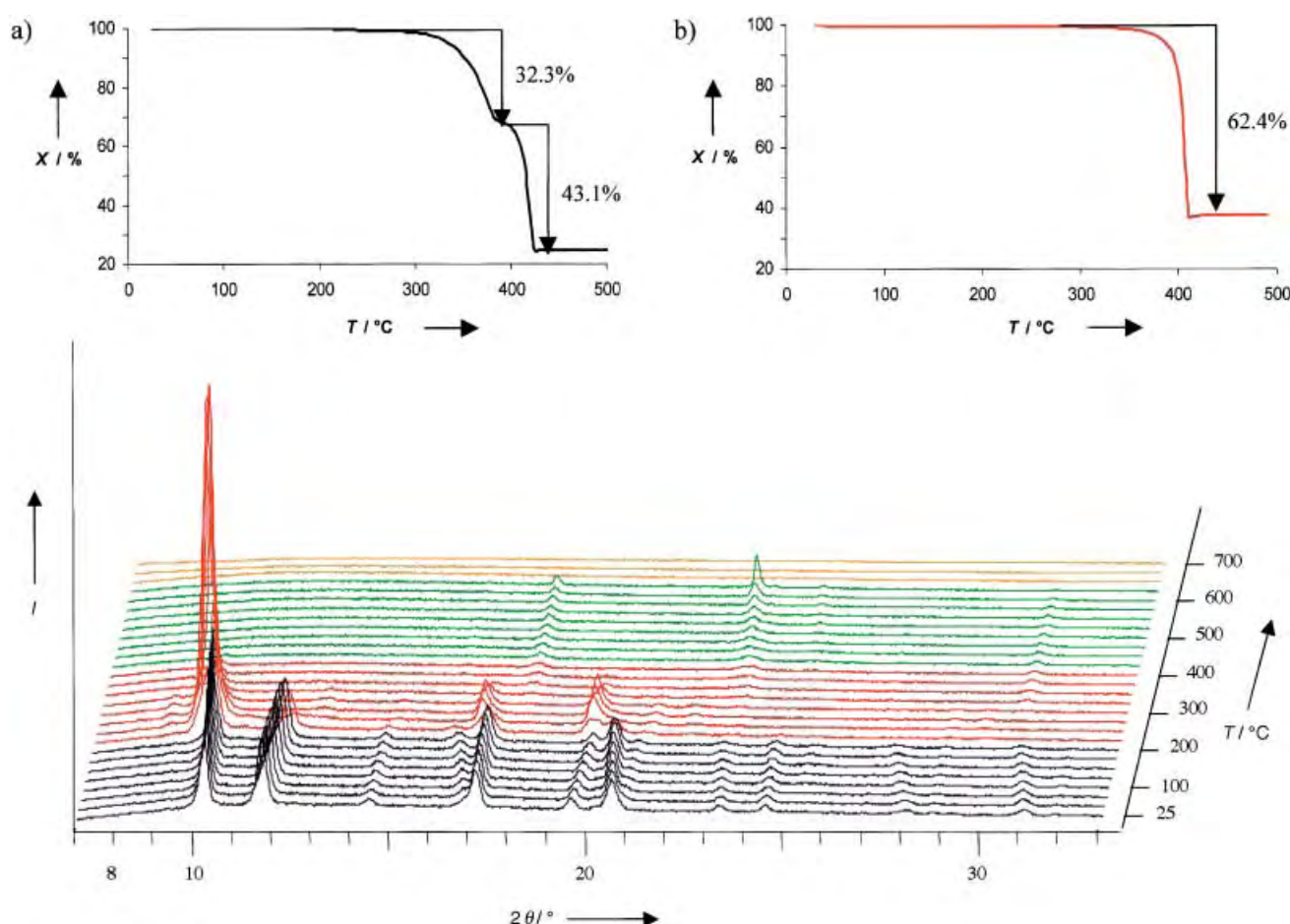


Figure 1. Thermogravimetric analysis of MIL-47as, showing the two steps of transformation. Inserts a) and b) give the thermogravimetric curves of MIL-47as and MIL-47, respectively.

$x = 0.75$ ) represents the evacuation of the terephthalic acid guest to produce the evacuated  $\text{V}^{\text{IV}}\text{O}[\text{O}_2\text{C}-\text{C}_6\text{H}_4-\text{CO}_2]$  (hereafter MIL-47) (vide infra). The second step (exp.: 43.1%, calcd: 40.30% for  $x = 0.75$ ) relates to combustion of the terephthalic acid of the framework. The residue is a mixture of  $\text{VO}_2$  and  $\text{V}_2\text{O}_5$ . Evacuated MIL-47 can be obtained pure by calcination (for 250 mg) 24 h under air at 573 K in a tubular furnace. MIL-47 decomposes at 673 K in one step (Figure 1 b). The experimental X-ray patterns are in excellent agreement with those calculated from single-crystal data.

Single crystals of both MIL-47as and MIL-47 were examined by X-ray diffraction.<sup>[6]</sup> Both solids present the same topology with a three-dimensional orthorhombic structure that exhibits large pores (free diameter taking account the Van der Waals radii:  $7.9 \times 12.0$  Å for MIL-47as and  $10.5 \times 11.0$  Å for MIL-47) in the [100] direction (Figure 2). Each tunnel is delimited by four walls of benzyl units and four chains of corner-shared vanadium octahedra (Figure 2). As shown by valence bond calculations<sup>[7]</sup> the shared vertices are hydroxy groups associated with  $\text{V}^{\text{III}}$  in MIL-47as and oxygen atoms associated with  $\text{V}^{\text{IV}}$  in MIL-47. The six V–O distances lie in the range  $1.946(2) - 1.998(2)$  Å, which is usual for  $\text{V}^{\text{III}}\text{--O}$  bonds, for MIL-47as. In MIL-47, along the chains, the alternation of short ( $1.672$  Å) and long ( $2.102$  Å) bonds is typical of  $\text{V}^{\text{IV}}$  in octahedral coordination. In MIL-47as, the terephthalic acid guest is highly disordered. Although its

refinement was not possible, chemical analysis, density measurements (exp.: 1.597(8); calcd: 1.613, Micromeritics multipycnometer), and the recrystallization of terephthalic acid in the cold parts of the apparatus during the degassing phase of MIL-47as for BET measurements confirm the hypothesis. The carboxylate groups of the framework terephthalate link two adjacent octahedra of one chain. The resulting strong tilting of the octahedra leads to a V–O–V superexchange angle of  $124.0(2)^\circ$  for MIL-47as and of  $129.38^\circ$  for MIL-47. Such a topology is close to that of  $[\text{CuSiF}_6(4,4'\text{-bipyridine})_2]_n$  previously described by Kitagawa et al.<sup>[5c]</sup> in which the chains are formed by alternation of  $\text{CuN}_2\text{F}_4$  and  $\text{SiF}_6$  octahedra linked by corners, leading to two-dimensional (2D) magnetic behavior.

At room temperature, the crystallinity of MIL-47 is preserved; density (calcd: 1.00) and thermogravimetric analysis (TGA) measurements indicate that it does not reabsorb atmospheric water. The permanent porosity of the evacuated MIL-47 was confirmed by gas sorption isotherm experiments performed (Micromeritics ASAP2010) in liquid nitrogen. While MIL-47as evidently does not present any capacity for  $\text{N}_2$  sorption, MIL-47 reveals a type I isotherm (Figure 3) without hysteresis upon desorption. The measured BET surface area is  $930(30) \text{ m}^2 \text{ g}^{-1}$  and, assuming monolayer coverage by  $\text{N}_2$ , the Langmuir surface area is estimated to be  $1320(2) \text{ m}^2 \text{ g}^{-1}$ .

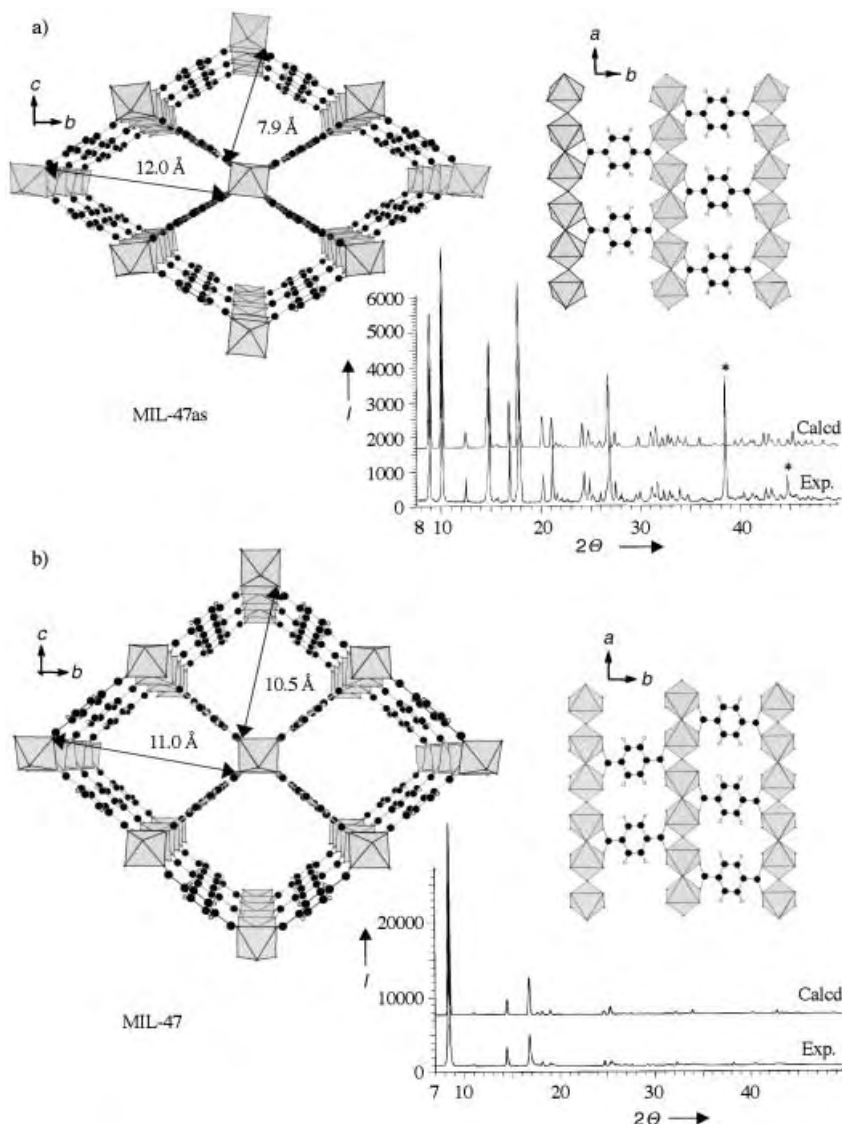


Figure 2. Projections of the structures of MIL-47as (a) and of MIL-47 (b), and X-ray powder patterns (experimental and calculated) of the two phases. Guest atoms in MIL-47as are omitted for clarity (\* peaks of the aluminum sample holder).

The noticeable flexibility of the framework with and without guest, deduced from the structure determinations, is easily evidenced by the evolution of the X-ray powder pattern (Figure 2) between the filled and evacuated phases. This

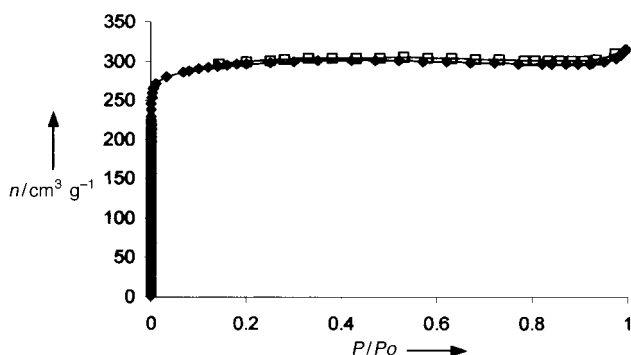


Figure 3.  $N_2$  sorption and desorption isotherms measured at 77 K for MIL-47 ( $\blacklozenge$  = sorption,  $\square$  = desorption;  $P_0 = 1$  atm).

allows us to monitor the desorption–adsorption of gases by evacuated MIL-47 by X-ray diffraction at room temperature. For instance, the readsorption of diethyl ether is achieved after 72 h. Guest exchange studies also show that the structural integrity of the framework is maintained in solution without any loss of crystallinity. Typically, introduction of MIL-47 in trimethylbenzene and 2-methyl-1-propanol gives the MIL-47as framework after reaction times that are dependent on the nature of the liquid, but which do not exceed 72 h.

Magnetic measurements performed on MIL-47as indicate (Figure 4) antiferromagnetic behavior below  $T_N = 95(5)$  K. The fit of the paramagnetic part of the  $1/\chi$  curve between 180 and 300 K with a Curie–Weiss law provides a paramagnetic temperature  $\theta_p$  of  $-186(4)$  K, indicative of strong antiferromagnetic interactions. The Curie constant of  $1.04(2)$  is typical of  $V^{3+}$  ions (theoretical value 1). According to Goodenough rules,<sup>[8]</sup>  $V^{3+} - V^{3+}$  interactions are predicted to be ferromagnetic if the superexchange angle is close to  $180^\circ$ , with vanadium in an octahedral coordination site but the sign of the exchange integral  $J$  can be inverted when the V–O–V angle decreases below the so-called “blank angle”. It is probably the case here, since the superexchange angle is only  $124^\circ$ , due to the effect of chelation by carboxylates between two octahedra. It is likely that this low value corresponds to antiferromagnetic interactions within and between chains. Otherwise, if  $124^\circ$  is larger than the blank angle, the magnetic structure would correspond to the antiferromagnetic coupling of ferromagnetic chains. The same behavior is observed with MIL-47 with a lower  $T_N$  ( $75(5)$  K) value, which is related to the weaker  $V^{4+} - V^{4+}$  ( $d^1 - d^1$ ) interactions. However, the striking feature that confirms our strategy is the drastic effect of  $\pi$  electrons on the temperature of magnetic ordering. Other structures, built with the same chains of  $V^{4+}$  ions with similar superexchange angles and interchain distances,<sup>[9]</sup> but without

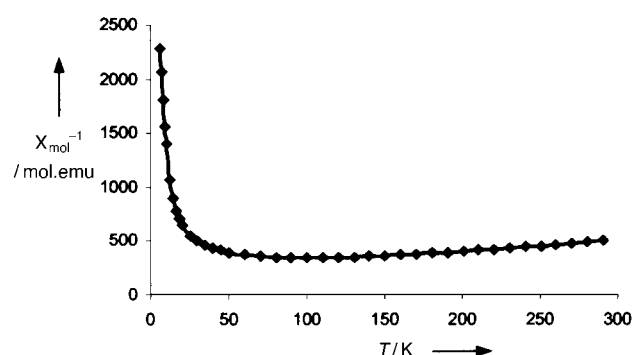


Figure 4. Reciprocal molar magnetic susceptibility as a function of the temperature for MIL-47as.

delocalized electrons on the linkers between the chains, exhibit very low  $T_N$  values (4–10 K). The presence of these  $\pi$  electrons drastically enhances the magnetic characteristics of these solids above the strategic borderline of liquid nitrogen temperature. This renders porous solids magnetic with sufficiently high and available ordering temperatures which could now find applications, for example, in magnetic sorting.

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## Infinite Secondary Building Units and Forbidden Catenation in Metal-Organic Frameworks\*\*

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Catenation, in the form of interpenetrating and interweaving,<sup>[1]</sup> has been a major concern in the design of low-density (porous) structures due to the following widely held beliefs: a) the use of long links for the design of frameworks with large pores results in catenated structures and thus small pores, b) highly catenated frameworks typically have low porosity (<20%), and c) catenation contributes negatively to the structural stability and porosity of open frameworks.<sup>[1, 2]</sup> We recently found in the chemistry of metal-organic frameworks (MOFs) that *discrete* secondary building units (SBUs) are important for designing structures with attributes that disprove the universality of b) and c); specifically, maximally interpenetrating MOFs have been shown to have highly porous (>65%) structures, and interweaving in open frameworks has been recognized and used for the design of structures with reinforced walls and permanent porosity.<sup>[1c–d, 3]</sup>

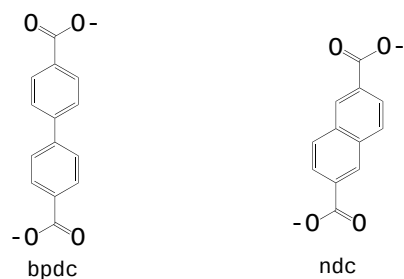
Herein, we introduce the use of *infinite* SBUs toward addressing the point presented in a). Specifically, we show that MOF-69A,  $[\text{Zn}_3(\text{OH})_2(\text{bpdc})_2] \cdot 4\text{DEF} \cdot 2\text{H}_2\text{O}$  (bpdc = 4,4'-biphenyldicarboxylate; DEF = *N,N'*-diethylformamide), and its 2,6-naphthalenedicarboxylate (ndc) analogue MOF-69B have three-dimensional (3D) structures constructed from infinite Zn-O-C SBUs and long bpdc or ndc links that expand the Al net in  $\text{SrAl}_2$  and provide a framework where catenation is forbidden.

Infinite Zn-O-C SBUs were produced by subjecting reaction mixtures that typically give MOF-5 to increasing amounts of  $\text{H}_2\text{O}_2$ .<sup>[4]</sup> These solutions were monitored for the appearance of crystalline solids. A single-crystal X-ray diffraction study<sup>[5a]</sup> performed on a rodlike colorless crystal of MOF-69A

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revealed the presence of a 3D network that is constructed from columns of Zn-O-C units running along the [001] direction (Figure 1a). In the asymmetric unit there are three crystallographically unique Zn atoms that are bridged in a dimonodentate fashion by four carboxylate groups, each from a different bpdc link. The Zn atoms are also bound to two hydroxy groups to give two tetrahedral and one octahedral Zn centers arranged in a coplanar fashion. Assignment of the bridging oxygen atom as a  $\mu_3$ -hydroxy group was confirmed by comparing the Zn-O(H)-Zn angles ( $93.7(3)$ ,  $110.2(5)$ ,  $110.3(5)^\circ$ ) in MOF-69A to those typically found in the analogous molecular Zn complexes containing  $\mu_3$ -hydroxy groups ( $103.3(1)$ ,  $110.7(2)$ ,  $112.2(2)^\circ$ ), in which the angles are close to the expected tetrahedral geometry rather than the trigonal-planar one generally observed for  $\mu_3$ -oxy groups.<sup>[6, 7]</sup> Interestingly, the Zn-O-C connectivity pattern observed in

MOF-69A is identical to the one observed in the structure of discrete basic zinc crotonate,  $[\text{Zn}_3(\text{OH})_2(\text{O}_2\text{CHCHCH}_3)_8]$ , in which similar  $\mu_3$ -hydroxy groups are also present.<sup>[6b]</sup>

The infinite Zn-O-C columns in MOF-69A are stacked in parallel and connected in the [110] direction by the biphenyl links to give one-dimensional (1D) rhombic channels of  $12.2 \text{ \AA}$  along an edge and  $16.6 \text{ \AA}$  along the diagonal<sup>[8]</sup> (Figure 1b) into which four DEF and two water molecules per formula unit reside as guests. Two DEF molecules were found hydrogen-bonded to  $\mu_3$ -hydroxy groups ( $\text{O}\cdots\text{H}\cdots\text{OC}$   $2.81 \text{ \AA}$  for MOF-69A), while the remaining two DEF and two water guests are disordered in the crystal, an aspect that facilitates their liberation from the pores (*vide infra*).

To fully appreciate the structure of MOF-69A and how its topology is a prototype for frameworks that *will not* catenate, it is instructive to connect all the points-of-extension (the carboxylate C atoms) in the structure. This gives a tetrahedral net with the C atoms at the vertices (Figure 1c). Closer examination of this net shows that the Zn-O-C columns become square ribbons, corresponding to the infinite SBUs, and the biphenyl units represent the lines that connect the SBUs together. This topology is identical to that of the Al net in  $\text{SrAl}_2$ .<sup>[9]</sup> However, unlike  $\text{SrAl}_2$ , MOF-69A has an open structure due to expansion of the Al net with Zn-O links (within the SBUs) and  $\text{C}_6\text{H}_4$ - $\text{C}_6\text{H}_4$  links (between the SBUs). Such an arrangement provides two important distances that impact catenation: a short distance between carboxylate C atoms along the [001] direction ( $5.839(3) \text{ \AA}$  and  $6.237(3) \text{ \AA}$ ), and a longer one in the [110] direction (between the SBUs) ( $10.069(4) \text{ \AA}$ ). The first distance allows the long links to come closer together such that the phenyl rings of each bpdc linker have a torsion angle of  $28.9(1)^\circ$  and, more significantly, form close mutual  $\text{CH}\cdots\pi$  interactions ( $3.73 \text{ \AA}$ ) to adjacent links resulting in an impenetrable wall of bpdc units (Figure 1d). For this structure to catenate, an additional bpdc would have to fit between adjacent links which is metrically impossible and thus results in a structure that forbids catenation.<sup>[10]</sup>

The implication of this finding is that linkers of longer lengths than bpdc and the same width (one benzene ring) can be employed in identical syntheses to produce the same framework but with correspondingly larger pores. As a first step in this direction, we have demonstrated that the infinite SBUs present in MOF-69A can be reproduced with ndc to give the isostructural compound formulated as  $[\text{Zn}_3(\text{OH})_2(\text{ndc})_2] \cdot 4\text{DEF} \cdot 2\text{H}_2\text{O}$  (MOF-69B).<sup>[5b]</sup>

Given that infinite SBUs heretofore have not been recognized and used in the context of design and construction of MOFs, we sought to probe the structural stability of MOF-69A and the mobility of the guests within its pores. Calculation of the pore

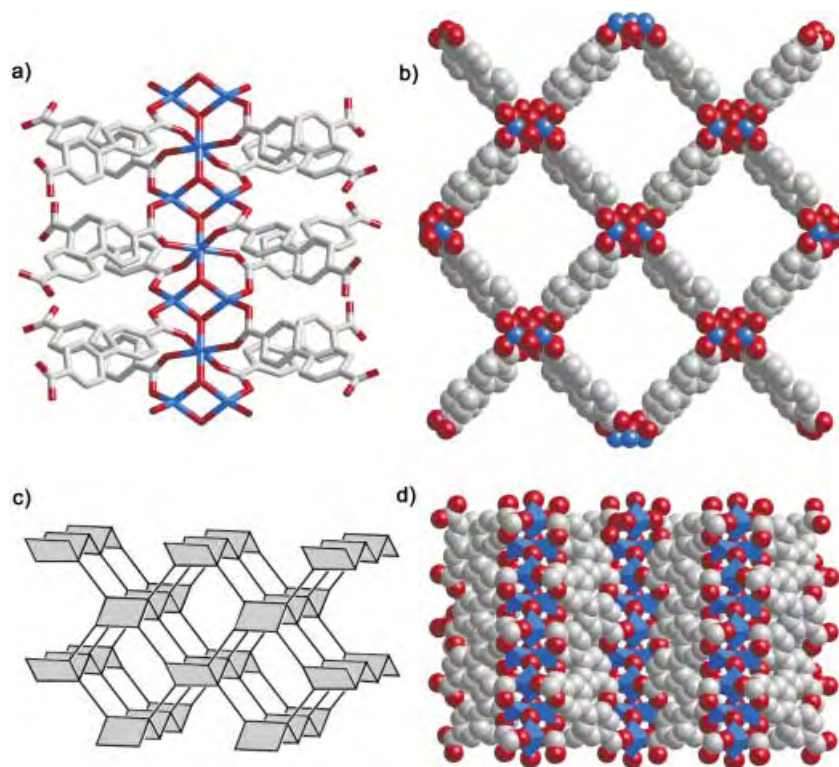


Figure 1. The crystal structure of MOF-69A,  $[\text{Zn}_3(\text{OH})_2(\text{bpdc})_2] \cdot 4\text{DEF} \cdot 2\text{H}_2\text{O}$ , containing a) infinite Zn-O-C SBUs that are linked together by bpdc links to form b) a 3D network with large channels running along the [001] direction (as shown) where the four DEF and two water guests per formula unit reside. c) This framework has the topology of the Al net in  $\text{SrAl}_2$ , which creates a structural arrangement where d) the walls of the channels are impenetrable as a result of close biphenyl-biphenyl  $\text{CH}\cdots\pi$  interactions leading to a structure motif that will not catenate regardless of the linker's length.

space in MOF-69A reveals that about 67% (66% for MOF-69B) of the structure is occupied by guest molecules.<sup>[11]</sup> Thermal gravimetric analysis (TGA) performed on a sample of the as-synthesized MOF-69A showed one sharp weight loss of 37.1% in the range 25–150 °C that continued slowly until 400 °C which is equivalent to the loss of four DEF and two water molecules per formula unit (calcd: 38.2%). For MOF-69B, two distinct weight loss steps were observed: 21.2% in the range 40–150 °C and an additional 19.1% in the range 150–400 °C, which correspond to the consecutive loss of two DEF and two water (calcd: 21.7%), and two DEF (18.4%) molecules, respectively. Presumably, the latter weight loss is due to the two strongly hydrogen-bonded DEF guests in the crystal structure of MOF-69B. This was unobserved as a distinct weight loss in MOF-69A perhaps due to weaker hydrogen-bonded interactions. It appears that the hydrogen-bonded DEF molecules are crucial to the stability of MOF-69, as illustrated by a variable-temperature X-ray powder diffraction (XRPD) study performed on both MOF-69A or B between 50 and 300 °C in 50 °C increments. Comparison of the XRPD patterns at these temperatures to those of the as-synthesized samples of MOF-69A and B showed that MOF-69A maintains its crystallinity up to 150 °C, while for MOF-69B a more complex behavior is observed: a new phase begins to emerge at 150 °C, which results from the loss of the non-hydrogen-bonded DEF and water guests. The original phase can be regained by introduction of DEF into solids of MOF-69B that have been heated up to 250 °C. For both MOF-69A and B heating above 150 °C and 250 °C, respectively, leads to an irreversible loss of crystallinity; specifically, attempts to regain crystallinity of the heated solids by reintroduction of DEF were unsuccessful, pointing to the importance of hydrogen-bonded DEF guests to the integrity of the structure.

MOF-69A and B are quite stable to exchange of guests in solution. Immersion of as-synthesized samples into benzene, chloroform, isopropanol, tetrahydrofuran, and toluene, typically overnight with three cycles of supernatant removal followed by fresh solvent addition, showed complete exchange of DEF.<sup>[12]</sup> The exchange process does not result in destruction of the framework as evidenced by XRPD, where the exchanged solids showed sharp XRPD lines albeit some shifts of the lines from their original position were observed. Preliminary evidence suggests that the shifts can be related to slight contraction of the framework in the [100] direction accompanied by corresponding elongation in the [011] direction. Further work is underway to quantitatively characterize these distortions. Nevertheless, the exchange process is fully reversible in that reintroduction of DEF into the channels gives an XRPD pattern identical to that of the starting MOF-69 material.

Encouraged by the solution–guest exchange and thermal stability, we attempted to evaluate the rigidity of the MOF-69A and MOF-69B frameworks. The samples were evacuated in a CAHN C1000 microbalance under reduced pressure ( $1 \times 10^{-5}$  Torr) until no more weight loss was observed. The evacuated sample was exposed to different gas and organic vapor sorbates using published protocol.<sup>[13]</sup> No sorption of N<sub>2</sub> or Ar was observed, possibly due to the flexibility of the framework. Nevertheless, we observed that benzene can be

sorbed into the pores of MOF-69B: exposure of an evacuated sample to near saturated benzene vapor pressure (65.7 Torr) resulted in 1.04 benzene molecules sorbed per formula unit.

We have demonstrated a strategy for realizing frameworks with large pores as exemplified by MOF-69 where a direct dependence is established between long links and the achievement of large pores, without the complications commonly observed due to catenation. Consideration of infinite SBUs in MOF-69 as rods or cylinders points to establishing design strategies based on rod packing for the synthesis of mesoscopic MOFs.

### Experimental Section

**MOF-69A:** A solid mixture of Zn(NO<sub>3</sub>)<sub>2</sub> · 6H<sub>2</sub>O (24.6 mg, 0.083 mmol) and H<sub>2</sub>bpdC (10 mg, 0.041 mmol) was dissolved in a vial containing DEF (12 mL), 30% H<sub>2</sub>O<sub>2</sub> (0.40 mL), and MeNH<sub>2</sub> (0.20 mL, 51.4 mM in DMF). The mixture was allowed to stand in a capped vial for seven days at room temperature. Colorless crystals of MOF-69A were collected and air-dried (21 mg, 86.1% yield). This compound is insoluble in water and common organic solvents. Elemental analysis calcd (%) for [Zn<sub>3</sub>(OH)<sub>2</sub>(bpdC)] · 4DEF · 2H<sub>2</sub>O: C 50.08, H 5.78, N 4.87, Zn 17.04; found: C 50.81, H 5.48, N 5.16, Zn 16.13.

**MOF-69B:** A solid mixture of Zn(NO<sub>3</sub>)<sub>2</sub> · 6H<sub>2</sub>O (24.6 mg, 0.083 mmol) and H<sub>2</sub>ndC (8.9 mg, 0.041 mmol) was dissolved in a vial containing DEF (12 mL), 30% H<sub>2</sub>O<sub>2</sub> (0.40 mL), and MeNH<sub>2</sub> (0.20 mL, 51.4 mM in DMF). The mixture was allowed to stand in a capped vial for seven days at room temperature. Colorless crystals of MOF-69B were collected and air-dried (18 mg, 80.4% yield). This compound is insoluble in water and common organic solvents. Elemental analysis calcd for MOF-69B, [Zn<sub>3</sub>(OH)<sub>2</sub>(ndC)] · 4DEF · 2H<sub>2</sub>O: C 48.08, H 5.69, N 5.10, Zn 17.85; found: C 48.28, H 5.13, N 5.02, Zn 17.76.

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isotropically. Hydrogen atoms were included in predicted positions for the ligand and the ordered DEF molecule but not refined. The final cycle of full-matrix least-squares refinement was based on 1339 observed reflections ( $I > 2.50\sigma(I)$ ) and 171 variable parameters and refined to convergence  $R_1 = 0.060$  and  $R_w$  (all data) = 0.066. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.64 and  $-0.55 \text{ e}^- \text{ \AA}^{-3}$ , respectively. While a hydrogen-bonded DEF molecule was defined well, the other DEF guest molecule was not modeled suitably due to the severe disorder around a mirror plane. b) Data collection for MOF-69B: A colorless needle crystal was analyzed: approximate dimensions:  $0.12 \times 0.020 \times 0.020 \text{ mm}$  at  $-115^\circ\text{C}$ , monoclinic, space group  $C2/c$  (no. 15) with  $a = 20.1658(15)$ ,  $b = 18.5518(14)$ ,  $c = 12.1580(9) \text{ \AA}$ ,  $\beta = 95.331(1)^\circ$ ,  $V = 4528.8(6) \text{ \AA}^3$ ,  $Z = 4$ ,  $\rho_{\text{calcd}} = 1.612 \text{ g cm}^{-3}$ , and  $\mu(\text{MoK}\alpha) = 16.54 \text{ cm}^{-1}$ ,  $F(000) = 2288$ , 4647 unique reflections within  $2\theta_{\text{max}} = 52.86^\circ$ ,  $T_{\text{max}} = 0.97$ ,  $T_{\text{min}} = 0.75$ . All non-hydrogen atoms were refined anisotropically. The hydrogen atoms of the ndc ligand and the six methyl hydrogen atoms in a DEF molecule were generated with idealized geometries. The hydrogen atoms in both the hydroxy group and the DEF molecule were found in the electron density map and their positional parameters were refined. The final cycle of full-matrix least-squares refinement was based on 2282 observed reflections ( $I > 2.00\sigma(I)$ ) and 294 variable parameters and refined to convergence  $R_1 = 0.0587$  and  $R_w = 0.1855$ . The maximum and minimum peaks on the final difference Fourier map corresponded to 0.854 and  $-0.761 \text{ e}^- \text{ \AA}^{-3}$ , respectively. c) All crystal structures in this report may be viewed and manipulated on the web: <http://www.umich.edu/~yaghigrp/structures.html> 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-170965 (MOF-69A) and CCDC-170966 (MOF-69B). 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](mailto:deposit@ccdc.cam.ac.uk)).

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## Photoresponsive Cyclic Bis(cysteiny)peptides as Catalysts of Oxidative Protein Folding\*\*

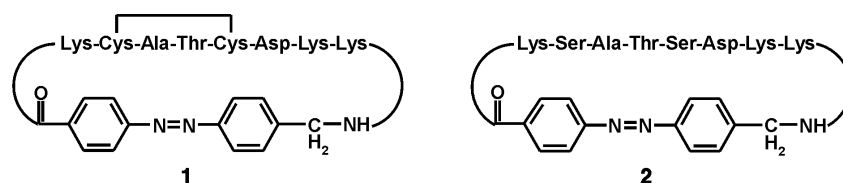
Anna Cattani-Scholz, Christian Renner, Chiara Cabrele, Raymond Behrendt, Dieter Oesterhelt, and Luis Moroder\*

Folding and disulfide bridging of cysteine-containing proteins are thermodynamically coupled, generally slow processes in which rapidly formed nonnative intermediates have to be reshuffled by redox systems into the native cysteine network.<sup>[1]</sup> Disulfide bond formation and rearrangement are catalyzed in vivo by specialized enzymes such as protein disulfide isomerase (PDI) in eukaryotes<sup>[2]</sup> and disulfide bond (Dsb) proteins in prokaryotes.<sup>[3]</sup> These enzymes belong to the thioredoxin superfamily, exhibit the thioredoxin fold,<sup>[4]</sup> and contain the active-site consensus motif Cys-Xaa-Yaa-Cys that is located at the N-terminus of an  $\alpha$ -helix. The cysteine residue nearer to the N-terminal of the two cysteine residues in the active site is solvent-exposed and because of its low  $pK_a$  value it acts as the nucleophile in the thiol/disulfide exchange reactions required for the correct oxidative folding pathway.<sup>[5]</sup> In vitro, the glutathione redox system (GSH/GSSG) is routinely used as auxiliary oxidative refolding agent<sup>[6]</sup> to mimic the natural environment in the endoplasmic reticulum,<sup>[7]</sup> and thus to allow through thiol/disulfide exchange reactions the thermodynamically most stable oxidation product to be formed, although often with significantly lower efficacy than in the presence of the thiol/disulfide oxidoreductases.

Despite the common thioredoxin fold, the thiol/disulfide oxidoreductases differ significantly in their redox potentials ( $E_0'$ ) ranging from  $-270$  mV for thioredoxin<sup>[8]</sup> to  $-122$  mV for DsbA,<sup>[9]</sup> as well as in the  $pK_a$  value of the N-terminal cysteine of the active site (3.5 for DsbA, 4.5 for PDI, and about 7 for thioredoxin).<sup>[9]</sup> These large differences in the redox and nucleophilic properties of the thiol functions have been attributed to the different sequences of the  $\alpha$ -helix-folded active-site motif,<sup>[8–10]</sup> whereas a decisive role of vicinal charged residues is more controversial.<sup>[11]</sup> In a previous study we analyzed whether the well differentiated redox properties of the enzymes of the thioredoxin family are retained in linear synthetic replicates of the active-site fragments.<sup>[12]</sup> Although the bis(cysteiny)peptides showed moderately different redox potentials, their values were all close to  $-200$  mV, thus enabling only minor catalytic effects on oxidative folding of RNase A as model protein.<sup>[13]</sup> These results clearly confirmed that the sequence-intrinsic free energy of formation of the disulfide-bridged Cys-Xaa-

Yaa-Cys motif as well as the  $pK_a$  values of the two thiol functions are significantly affected and amplified by the structural constraints imparted by the overall protein fold. Consequently, conformationally restricted cyclic bis(cysteiny)peptides might mimic in a more appropriate manner the active sites of the enzymes in terms of redox properties and disulfide reshuffling activity. In fact, cyclization of the active-site fragments mentioned above led to significantly more oxidizing redox potentials (unpublished results).

Backbone cyclization of the active-site fragment *H*-Ala-Cys-Ala-Thr-Cys-Asp-Gly-Phe-*OH* [134–141] of *E. coli* thioredoxin reductase by the photoresponsive 4-(4-aminophenylazo)benzoic acid or 4-(4-(aminomethyl)phenylazo)benzoic acid led to peptide systems that are characterized by a fully reversible *cis*  $\leftrightarrow$  *trans* photoisomerization of the azobenzene moiety.<sup>[14]</sup> This isomerization is accompanied both in the reduced monocyclic and oxidized bicyclic form by conformational transitions. The low-energy structures of *trans* azo isomers are well-defined whereas *cis* azo isomers are less restricted conformational ensembles.<sup>[15]</sup> Owing to the water insolubility of these photoresponsive cyclic peptides, in the present study a water-soluble cyclic peptide was synthesized by appropriately replacing three residues outside the Cys-Ala-Thr-Cys motif with lysines (**1**, Scheme 1). Photomodulation of the redox properties of this analogue in aqueous media



Scheme 1. Structures of synthetic cyclic peptides related to the active site of *E. coli* thioredoxin reductase and containing 4-(4-aminomethyl)phenylazo)benzoic acid as backbone constituent.

was attained and exploited to differently affect rates and efficacy of oxidative folding of RNase A in redox buffer.

To unambiguously characterize the NMR solution conformation of the cyclic bis(cysteiny)peptide in its oxidized and reduced state as *trans* and *cis* isomer,<sup>[16]</sup> in addition to the bicyclic compound **1**, the related monocyclic bis(seryl)peptide **2** (Scheme 1) was synthesized<sup>[17]</sup> as the isomorphous analogue of the reduced bis(cysteiny)peptide. The Cys  $\rightarrow$  Ser replacement assures full stability under the non-strictly anaerobic conditions of the NMR experiments. As already observed in our previous study for the water-insoluble cyclic azobenzene peptides in DMSO,<sup>[15]</sup> the NMR-derived conformations of both compounds **1** and **2** in the *trans*-azo configuration are mainly dictated by the extended structure of the chromophore which stretches the C-terminal portion of the peptide into a parallel alignment to the azobenzene moiety and allows a bending only in the N-terminal part as imposed by the cyclic structure of the construct rather than by the disulfide bridge (Figure 1). In fact, in the absence of a disulfide bond and, thus, upon relief from the conformational restrictions imparted by the 14-membered ring, that is in the bis(seryl) analogue **2**, the overall structure is largely retained. The side chains of the two cysteine residues, mimicked by the serine residues in com-

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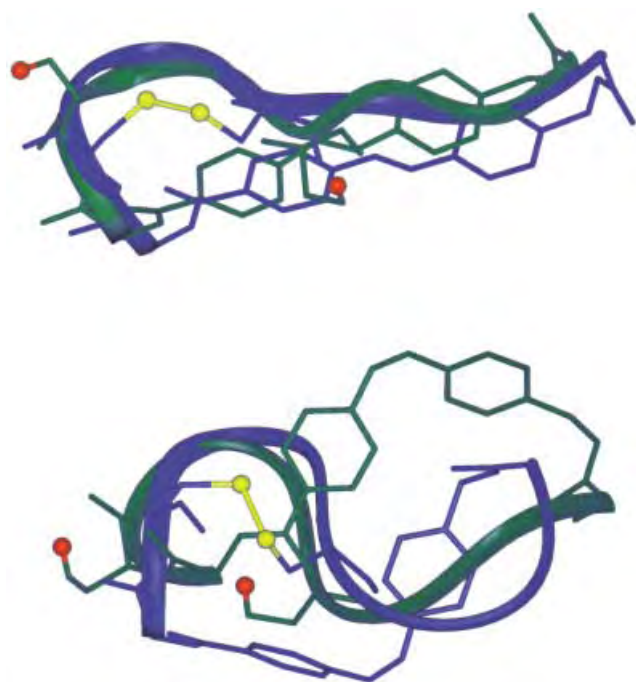


Figure 1. Representative structures from the lowest energy conformational families in aqueous solution derived from NMR conformational analysis of the *trans* isomers (top) and *cis* isomers (bottom) of the bicyclic compound **1** and the bis(seryl)peptide **2** as mimic of the reduced compound **1**. Backbone conformations are shown as ribbons, and the cysteine/serine residues as well as the azobenzene moiety as ball-and-stick models: blue for **1** and green for **2**.

pound **2**, are released from the ring-structure into the bulk water with minimal translational and rotational motions of the peptide backbone. Conversely, in the *cis*-azo configuration the bent structure of the chromophore significantly enhances the conformational freedom of the peptide moiety in both the monocyclic (**2**) and bicyclic (**1**) compounds. This favors in compound **1** the onset of a more helix-like turn involving the Cys-Ala-Thr-Cys motif, but the restraints of the disulfide bridge lead to an overall frustrated system that flip-flops between multiple conformational states. In the monocyclic peptide **2** a significantly more convergent family of energetically relaxed conformers is observed which are characterized by an S-shaped conformation. This is further supported by the observation that the activation energy of the thermal *cis* → *trans* isomerization of the monocyclic compound **2** is 12 kJ higher than that of the oxidized bicyclic form **1**.

As observed for the analogous systems in DMSO,<sup>[15]</sup> the *trans* ↔ *cis* photoisomerization of compound **1** upon irradiation at 360 nm and 450 nm, respectively, is fully reversible and occurs with high quantum yields following first-order kinetics with two isosbestic points located at 396 nm and 291 nm, respectively. Based on these photoresponsive properties as well as on the slow thermal relaxation of the isomerization in the darkness at room temperature, the redox properties of compound **1** in the *trans*-azo and *cis*-azo configuration were analyzed.<sup>[18]</sup> For this purpose, thiol/disulfide exchange experiments were performed with GSH/GSSG as reference redox pair, as previously described for the linear active-site fragments of the enzymes of the thioredoxin

family.<sup>[12a]</sup> A typical chromatograph (HPLC) of the redox mixture of the *cis* and *trans* isomers with excess glutathione is shown in Figure 2. Reproducible  $K_{ox}$  values were obtained at

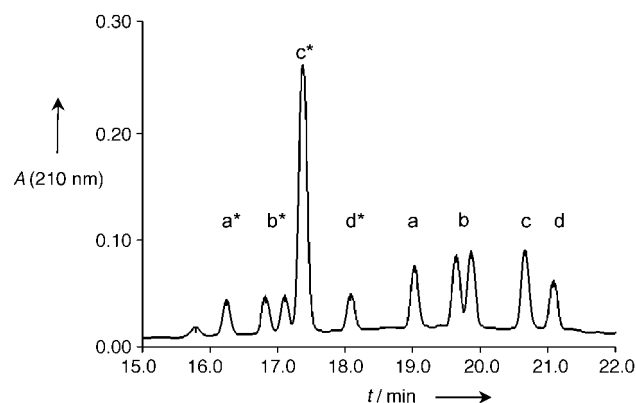


Figure 2. Chromatogram (HPLC) of an equilibrated redox mixture of **1** (*cis/trans* isomers) with excess glutathione (see ref. [18]). The species relative to the *cis*-azo configuration are marked by \*: a) mixed bis(glutathione)/peptide disulfide; b) a pair of mixed mono(glutathione)/peptide disulfides; c) reduced peptide, and d) oxidized peptide.

different GSH/GSSG ratios from which the average redox potentials were derived by using  $E'_0 = -240$  mV for glutathione<sup>[19]</sup> (Table 1). Despite cyclization and incorporation of three lysine residues, the *trans* isomer exhibits a redox potential of  $-200$  mV which differs only marginally from that of the parent linear active-site fragment *H*-Ala-Cys-Ala-Thr-Cys-Asp-Gly-Phe-*OH* [134–141] ( $-210$  mV),<sup>[12a]</sup> con-

Table 1. Apparent redox potentials of the linear and cyclic active-site peptides of *E. coli* thioredoxin reductase.

| Compound                                            | $K_{ox}$ [M]          | $E'_0$ [mV]  |
|-----------------------------------------------------|-----------------------|--------------|
| thioredoxin reductase                               |                       | $-250^{[a]}$ |
| linear active-site fragment [134–141]               | 0.123 <sup>[b]</sup>  | $-210^{[b]}$ |
| cyclic peptide <b>1</b> as <i>trans</i> -azo isomer | 0.050 <sup>[c]</sup>  | $-200^{[c]}$ |
| cyclic peptide <b>1</b> as <i>cis</i> -azo isomer   | 0.0008 <sup>[c]</sup> | $-146^{[c]}$ |

[a] Determined at pH 7.<sup>[21]</sup> [b] Determined in 0.1M phosphate buffer containing 0.1M NaCl and 1 mM EDTA (pH 7.0) at 20 °C and referred to a redox potential of  $-240$  mV for GSH/GSSG.<sup>[12a]</sup> [c] Determined in the present study in 0.1M phosphate buffer containing 0.1M NaCl and 1 mM EDTA (pH 7.0) at 25 °C using  $E'_0 = -240$  mV for GSH/GSSG.<sup>[18, 19]</sup> The  $K_{ox}$  and  $E'_0$  values are the average of three experiments.

firming the minor effect of charged residues on the redox potentials.<sup>[11]</sup> Conversely, in the *cis*-azo configuration the redox potential is significantly shifted to a more oxidizing value ( $E'_0 = -146$  mV), which makes the peptide system more similar to the native enzymes PDI ( $E'_0 = -147/-159$  mV) and DsbA ( $E'_0 = -122$  mV).<sup>[9]</sup> These differences in the redox potentials between the *trans* and *cis* isomers correlate well with the NMR conformational analysis. In the *trans*-azo configuration both the oxidized and reduced species show a very similar overall conformation and the free energy of formation of the 14-membered ring in the oxidized form should be mainly dictated by the entropic contributions associated with the proximal display of the two cysteine side

chains, while the conformational enthalpy and entropy terms should affect only marginally the  $K_{ox}$  value. In the *cis*-azo configuration, however, formation of the disulfide bridge is highly unfavorable, with a  $K_{ox}$  value that is nearly three orders of magnitude lower than that of the *trans* isomer. This lower propensity for the bicyclic state may be attributed to the penalty by the large conformational entropy change deriving from freezing the cysteine side chains into a defined topology, which is not compensated by a favorable conformational enthalpy term. In fact, a transition takes place from a lower energy conformation to a frustrated system in the oxidized form, as the lower activation energy for the *cis*  $\rightarrow$  *trans* thermal relaxation of **1** shows. An additional contribution to the difference in the redox potentials and a possible effect on the  $pK_a$  values of the two thiols might also arise from electronic contributions of the azobenzene moiety that is spatially displayed in a significantly different mode in the *trans*-azo and *cis*-azo configuration relative to the disulfide group. Because of the sensitivity of the azobenzene group toward strong reducing agents such as 1,4-dithiothreitol (DTT) or tricarboxyethylphosphane, quantitative reduction of the cystine system in **1** for the measurement of the thiol  $pK_a$  values was prevented. In this context it is worthy to note that the  $pK_a$  values of the two cysteine residues in the cyclic bis(cysteiny)lpeptides mentioned above are approximately 8 and 10, respectively, independent of the redox potentials that range from  $-130$  mV to  $-200$  mV (unpublished results).

Generally high redox potentials, low thiol  $pK_a$  values, and the presence of a peptide binding site, that is a chaperone activity that enables preferred interactions with the substrate, are the major features of natural protein disulfide isomerases. Although small bis(cysteiny)lpeptide systems cannot be expected to exert chaperone activity, their redox properties and  $pK_a$  values of the thiols should govern the catalytic efficiency in the oxidative folding processes of proteins. This catalytic effect on the oxidative refolding of reduced and denatured RNase A was analyzed for **1** in the *trans*-azo and *cis*-azo configuration.<sup>[20]</sup> For this purpose nonoptimal GSH/GSSG concentrations, that is an RNase A/GSH/GSSG ratio of 1:20:4, were used to avoid a buffering effect of glutathione on the auxiliary catalyst **1**. As shown in Figure 3, by replacing one equivalent of GSSG with **1** as *cis* isomer an acceleration of the initial rate of activation by 30% is obtained and, more significantly, the yield of active RNase A is increased from 56% to 80% after 30 h, with an extrapolated maximal reactivation of 94% ( $\pm 3\%$ ) versus 64% ( $\pm 2\%$ ) in the absence of **1**. Conversely, by replacing the *cis* isomer with the *trans* isomer the initial folding rate remains unaffected, but the refolding efficiency of the redox system is enhanced (extrapolated maximal reactivation of  $83\% \pm 3\%$ ). The latter effect may derive from the higher nucleophilicity of at least one of the two peptide thiols compared to glutathione, as it can be expected by analogy to the differentiated  $pK_a$  values of the cyclic bis(cysteiny)lpeptides mentioned above. An increase in the amount of compound **1** as *cis* isomer in the refolding mixture to two equivalents leads to a further acceleration of the initial folding rate (52% higher compared to the GSH/GSSG system). In contrast, increase in the concentration of the *trans* isomer is accompanied only by an

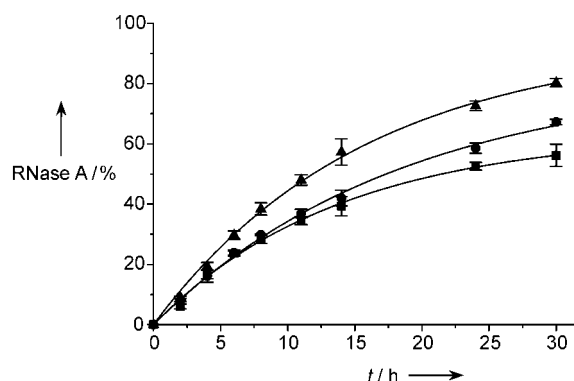


Figure 3. Time-course for the reactivation of reduced RNase A at 30°C and pH 7.4 with glutathione at an RNase A/GSH/GSSG molar ratio of 1:20:4 (■), glutathione plus **1** as *trans* isomer (●) or *cis* isomer (▲) at an RNase A/GSH/GSSG/**1** molar ratio of 1:20:3:1. Each point is the average value from three experiments. The data points are fitted to the equation  $[\text{active RNase A}]_t/[\text{reduced RNase A}]_{t=0} = a(1 - e^{-kt})$ , where  $a$  is the extrapolated maximal reactivation and  $k$  the first-order kinetic constant.

increase in the yield of the process, with an extrapolated maximal reactivation of 100%.

The experimental results confirm that conformationally restricted bis(cysteiny)lpeptide systems can mimic the active sites of thiol/disulfide oxidoreductases and exert disulfide isomerization activity that are reminiscent of the foldase properties of the natural protein disulfide isomerases. Moreover, by incorporation of the azobenzene moiety into the cyclic bis(cysteiny)lpeptide, a photomodulation of the efficiency of such folding adjuvants was achieved, a fact that may offer the possibility of a time-resolved modulation of functional properties.

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- [17] The linear peptide precursors were synthesized on chlorotriptyl resin by using the 9-fluorenylmethoxycarbonyl (Fmoc)/*t*Bu chemistry as described in reference [14]. Cyclization of the resulting side chain protected peptides was performed in DMF at a concentration of 0.5 mM by PyBOP/HOBt (benzotriazolyl-1-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate/1-hydroxybenzotriazole), and deprotection was carried out with trifluoroacetic acid/CH<sub>2</sub>Cl<sub>2</sub> (95:5) containing triethylsilane as scavenger. Oxidation of the cyclic bis(cysteiny)l peptide was performed by air-oxygen in ammonium acetate buffer (pH 8) at a concentration of 10<sup>−4</sup> M. **1**: ESI-MS: *m/z*: 1113.6 [*M*+H<sup>+</sup>]; *M<sub>r</sub>* = 1112.4 calcd for C<sub>49</sub>H<sub>72</sub>N<sub>14</sub>O<sub>12</sub>S<sub>2</sub>; amino acid analysis (6 M HCl, 110 °C, 24 h): Asp 1.00 (1), Thr 0.90 (1), Ala 0.97 (1), Cys 1.46 (2), Lys 2.95 (3); peptide content: 71 %. **2**: ESI-MS: *m/z*: 1085.8 [*M*+H<sup>+</sup>]; *M<sub>r</sub>* = 1082.6 calcd for C<sub>49</sub>H<sub>74</sub>N<sub>14</sub>O<sub>14</sub>; amino acid analysis (6 M HCl, 110 °C, 24 h): Asp 1.00 (1), Thr 0.99 (1), Ser 1.98 (2), Ala 0.98 (1), Lys 2.90 (3); peptide content: 75 %.
- [18] For the determination of the *K<sub>ox</sub>* values, the *trans* isomer and mixtures of the *cis/trans* isomers of **1** (0.1 mM) in argon-saturated 0.1 M phosphate buffer (pH 7) containing 0.1 M NaCl and 1 mM EDTA were equilibrated at 25 °C for 3–4 h under argon with 100-fold excess glutathione at varying GSH/GSSG ratios. Aliquots of the equilibrated redox mixtures were quenched with 1 M phosphoric acid and analyzed by HPLC. Baseline separation of all components was achieved and these were identified as the two sets of the *cis* and *trans* isomer species by ESI-MS and by comparison with the redox mixture obtained for the pure *trans* isomer (see Figure 2). The concentrations of the oxidized and reduced forms of **1** at equilibrium were obtained by integration of the corresponding HPLC peak areas.
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- [20] Fully reduced and denatured RNase A was prepared from bovine pancreatic RNase A (Aldrich, approximately 100 Kunitz units mg<sup>−1</sup> protein) and refolding assays were performed following essentially the protocols previously described (Y. Konishi, T. Ooi, H. A. Sheraga, *Biochemistry* **1982**, *21*, 4734–4740). Reoxidation of the reduced RNase A (24 μM) in 0.1 M Tris-HCl buffer, 1 mM EDTA, pH 7.4, was carried out at 30 °C under argon in the glutathione redox buffer at an RNase A/GSH/GSSG molar ratio of 1:20:4 and in the presence of **1** at an RNase A/GSH/GSSG/**1** molar ratio of 1:20:3:1 and 1:20:2:2. Compound **1** was used as *trans* isomer (100% after thermal relaxation at 50 °C overnight) and, upon irradiation at 360 nm, in the *cis*-azo configuration, that is in the photostationary state (*cis/trans* ratio: 80:20 ± 3). The reactivation reactions were initiated by addition of RNase A to the preequilibrated (at least 2 h at room temperature)

refolding mixtures. The samples with the *cis* isomer were irradiated at 360 nm for 4 min every 2 h over 14 h and for a further 4 min after 21 h and 28 h. The time course of correctly folded RNase A was determined by measuring on aliquots of the refolding mixtures the initial rates of enzymatic cCMP hydrolysis (432 μM in 0.1 M MOPS buffer, pH 7.0) at 284 nm and at a final RNase A concentration of 1.7 μM.

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## Oligo(phenylenevinylene)s with Terminal Donor–Acceptor Substitution\*\*

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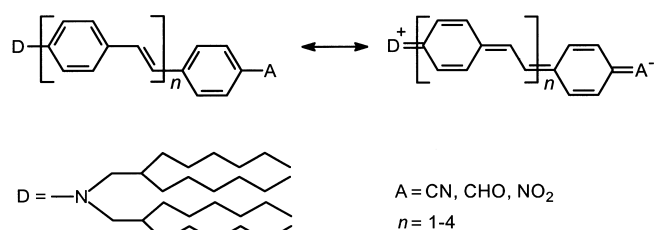
Conjugated oligomers<sup>[1]</sup> such as the oligo(phenylenevinylene)s (OPV)s have been extensively investigated for a number of years because they exhibit properties of interest to materials science in regard to application in nonlinear optics (NLO) and as photoconductors and electroluminescent devices. Typical of such a class of compounds is the convergence of absorption and fluorescence with the increasing number *n* of repeating units.<sup>[2]</sup> The determination of the effective conjugation length (ECL)<sup>[1a]</sup> is important for the characterization of the oligomers, as well as for their function as model compounds for the corresponding polymers. A simple algorithm, based upon exponential functions as natural growth functions, has been demonstrated to be effective for the determination of convergence and ECL in more than 20 series of conjugated compounds.<sup>[3]</sup>

We recently demonstrated that with a terminal push–pull substitution of conjugated oligomers the expected monotonic bathochromic shifts of absorption and fluorescence with increasing number *n* of repeating units need not necessarily be present.<sup>[4]</sup> Since such series are very important, especially for NLO materials, we have investigated the effect more thoroughly. OPV systems were prepared which have solubilizing bis(2-hexyloctyl)amino residues as the donor (D). Different acceptors (A) were introduced at the other end of the OPV chain (Scheme 1). The involvement of zwitterionic resonance structures should have a decisive influence upon

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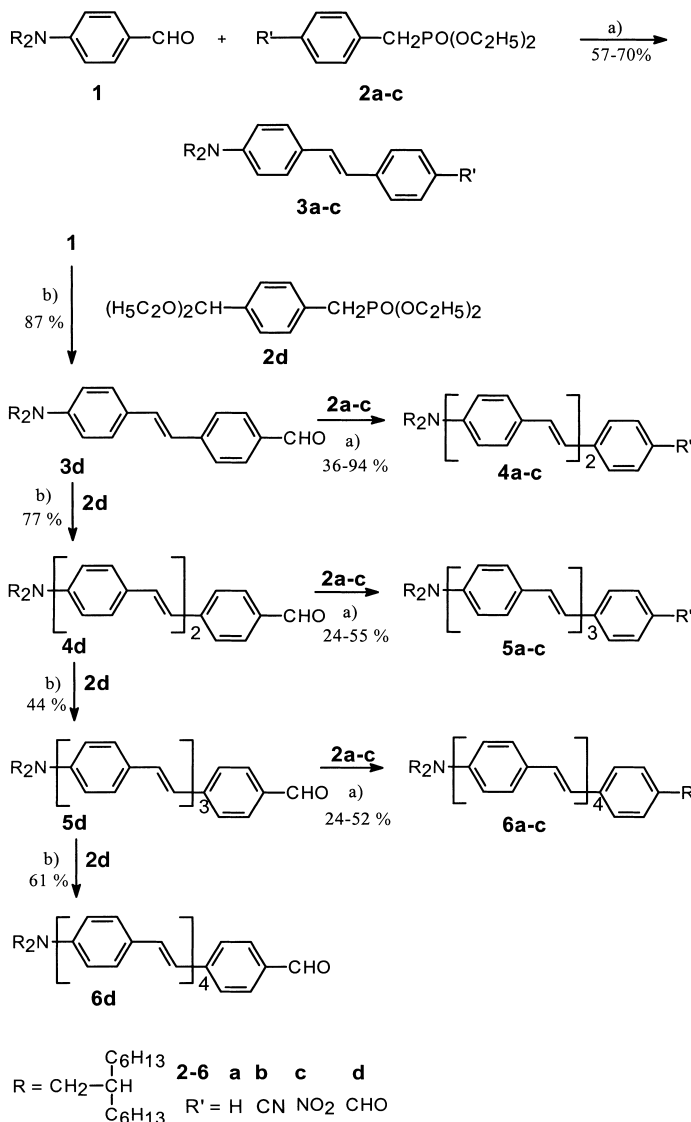
[\*\*] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



Scheme 1. Donor-acceptor substituted OPV systems

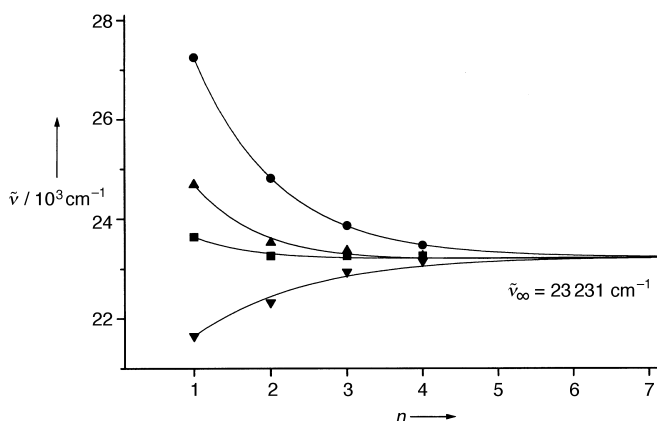
the electronic transitions; the solely donor substituted series ( $A = H$ ) serves as a reference series.

The preparation of monodisperse, configurationally pure oligomers was carried out by a convergent-synthesis strategy outlined in Scheme 2. 4-Bis(2-hexyloctyl)aminobenzaldehyde (**1**) was converted into the monostilbenes **3a–c** with the phosphonates **2a–c**, and also used for the construction of the "styrylogous" aldehydes **3d–6d**, the latter was by a repetitive Wittig–Horner reaction with the phosphonate **2d** and a


 Scheme 2. Preparation of the OPV series **3–6**. a) NaH, DME; b) 1)  $KOC(CH_3)_3$ , THF; 2) HCl.

simple protecting-group technique.<sup>[5]</sup> Each new aldehyde stage **3d–5d** was then converted into the target compounds **4a–c**, **5a–c**, and **6a–c** with **2a–c**.

Figure 1 shows the long-wavelength maxima of the donor-substituted series **3a–6a** and the donor-acceptor substituted series **3b–6b**, **3c–6c**, and **3d–6d**. With each additional  $n$  the terminal acceptors lead to a marked bathochromic shift of the push-pull systems relative to the purely donor-substituted


 Figure 1. Long-wavelength absorption maxima of the OPV series **3a–6a** (●), **3b–6b** (▲), **3c–6c** (▼), and **3d–6d** (■) in  $CHCl_3$  and fitting of the Equation (1).<sup>[7]</sup>  $\tilde{\nu}_\infty$  = common convergence limit.

series **3a–6a**. Most pronounced is the effect of the nitro group, the strongest acceptor. In contrast to the OPV series previously investigated,<sup>[2, 6]</sup> with terminal push-pull substituents a charge transfer occurs during the electron transition. The monotonic reduction in excitation energies (bathochromic effect) with increasing  $n$  is in line with expectations in the two series **3a–6a** and **3b–6b**; in the series **3d–6d**  $\tilde{\nu}_{max}$  is surprisingly almost independent of  $n$ , and in the series **3c–6c** the effect is even reversed: with **3c–6c** an increase in conjugation leads to a pronounced hypsochromic shift. With increasing  $n$  all four series converge towards the convergence limit  $E_\infty$  of the donor-substituted series **3a–6a**.

How may the different behavior of the donor-acceptor substituted series be explained? It may be concluded from the common convergence limit that with longer OPV chains the acceptor group plays no role in the absorption. Therefore, we have split the energy values of the electron transitions  $E_{DA}(n)$  into two components. The first term  $E_D(n)$  corresponds to the normal behavior of the purely donor-substituted series **3a–6a**, that is, to the expected bathochromic shift with increase in conjugation. The second term  $\Delta E_{DA}(n)$  is a correction term for the superimposition of the intramolecular charge transfer (ICT) in the push-pull substituted series. Both terms can be described by exponential functions<sup>[2]</sup> [Eq. (1)].

$$E_{DA}(n) = E_D(n) - \Delta E_{DA}(n) = E_\infty + [E_D(1) - E_\infty]e^{-a(n-1)} - [E_D(1) - E_{DA}(1)]e^{-\Delta a(n-1)} \quad (1)$$

Table 1 gives an overview of the measured absorption maxima and the parameters from the fitting for convergence with increasing  $n$ . The charge-transfer correction term  $\Delta E_{DA}(n)$  is always greatest at  $n = 1$ . With increasing separa-

Table 1. Long-wave absorption maxima ( $\tilde{\nu}_{\max}$  [cm<sup>-1</sup>],  $\epsilon_{\max}$  [cm<sup>2</sup>mmol<sup>-1</sup>]) of the OPV series **3a–6a**, **3b–6b**, **3c–6c**, and **3d–6d** in CHCl<sub>3</sub> and parameters from the fitting of Equation (1).<sup>[a]</sup>

| Compound                                 | <i>n</i> | Series <b>a</b>      |                   | Series <b>b</b>      |                   | Series <b>c</b>      |                   | Series <b>d</b>      |                   |
|------------------------------------------|----------|----------------------|-------------------|----------------------|-------------------|----------------------|-------------------|----------------------|-------------------|
|                                          |          | $\tilde{\nu}_{\max}$ | $\epsilon_{\max}$ | $\tilde{\nu}_{\max}$ | $\epsilon_{\max}$ | $\tilde{\nu}_{\max}$ | $\epsilon_{\max}$ | $\tilde{\nu}_{\max}$ | $\epsilon_{\max}$ |
| <b>3</b>                                 | 1        | 27248                | 19483             | 24691                | 21711             | 21645                | 28789             | 23641                | 20462             |
| <b>4</b>                                 | 2        | 24814                | 29711             | 23529                | 48107             | 22321                | 35425             | 23256                | 46822             |
| <b>5</b>                                 | 3        | 23866                | 68944             | 23364                | 63341             | 22936                | 58760             | 23256                | 67320             |
| <b>6</b>                                 | 4        | 23474                | –                 | 23256                | 86164             | 23148                | 95860             | 23256                | 84882             |
| Parameters                               |          |                      |                   |                      |                   |                      |                   |                      |                   |
| $E_{\infty}$ [cm <sup>-1</sup> ]         |          | 23231 ± 12           |                   | 23231 ± 12           |                   | 23231 ± 12           |                   | 23231 ± 12           |                   |
| $E_D(1) - E_{DA}(1)$ [cm <sup>-1</sup> ] |          | –                    |                   | 2557                 |                   | 5603                 |                   | 3607                 |                   |
| <i>a</i>                                 |          | 0.93 ± 0.01          |                   | 0.93 ± 0.01          |                   | 0.93 ± 0.01          |                   | 0.93 ± 0.01          |                   |
| $\Delta a$                               |          | –                    |                   | 0.76 ± 0.04          |                   | 0.86 ± 0.03          |                   | 0.87 ± 0.02          |                   |

[a] Curve fitting was carried out with the program Origin 5.0.

tion of donor and acceptor it falls exponentially towards zero, for example, from 5603 cm<sup>-1</sup> for **3c**, through 2493 and 930 to 326 cm<sup>-1</sup> for **6c** in the NO<sub>2</sub> substituted series. This reduction cannot be offset by the opposing effect which is a result of the extension of conjugation and is represented by  $E_D(n)$ . The nitro-substituted series consequently shows a hypsochromic shift for increasing *n*. In contrast the cyano-substituted series exhibits significantly smaller correction terms  $\Delta E_{DA}(n)$ , which moreover decrease more slowly with increasing *n*, from 2557 cm<sup>-1</sup> at *n* = 1 to 218 cm<sup>-1</sup> at *n* = 4. In this case the bathochromic effect on extending conjugation can overcompensate the decreasing charge-transfer term and in the summation the expected bathochromic shift is observed. In the series **3d–6d** the conjugation effect and the charge-transfer effect offset each other almost completely so that  $\tilde{\nu}_{\max}$  is almost independent of *n*.

How may this theory, on the basis of empirical fit functions, be supported quantum mechanically? We have calculated the frontier orbitals of **3a–c**, **4a–c**, **5a–c**, and **6a–c** by AM1 and INDO/S methods.<sup>[8, 9]</sup> A selection of these is reproduced in Figure 2. The long-wavelength electron transitions of the OPV systems are essentially HOMO → LUMO transitions for *n* = 1. The HOMO → LUMO energy difference decreases for

*n* = 1 (and also for each higher *n*) in the sequence **a** > **b** > **c**. Since the exchange integral for the electron correlation also decreases in this sequence because of the decreasing transition density, a bathochromic shift in the absorption for every *n* in the change from A = H, through A = CN, to A = NO<sub>2</sub> results. Within the series **a**, **b**, and **c** the HOMO → LUMO energy difference decreases with increasing *n*. However, the electron correlation leads then to smaller Coulomb integrals for the repulsion with increasing size of the chromophore, and therefore, to an opposing tendency. Thus, in principle, with increasing *n* in the oligomer series either a bathochromic or a hypsochromic shift of the absorption can occur.

With increasing *n* the fraction of HOMO → LUMO transitions in the long-wavelength absorption falls drastically; above all the electron transitions NHOMO → LUMO, HOMO → NLUMO, and NHOMO → NLUMO intermix (where N = next-to-). However, as Figure 2 shows, the HOMO → LUMO fraction is essentially determinative for charge transfer. If the ICT correction term  $\Delta E_{DA}(n)$  is now plotted against the involvement of the HOMO → LUMO transition calculated by the INDO/S method a simple correlation is recognized: the greater  $\Delta E_{DA}(n)$  for the charge transfer is, the greater the HOMO → LUMO contribution to the long-wavelength electron transfer is (Figure 3). Thus semi-empirical quantum mechanics reproduces correctly the observed trend: with increasing *n* the HOMO → LUMO contribution decreases, and with it the  $\Delta E_{DA}$ ; this effect dominates in the nitro-substituted series **3c–6c** and hence leads to the hypsochromic shift—in contrast in the cyano-substituted series **3b–6b** the term  $E_D(n)$ , which expresses the extension of the conjugation, dominates such that a bathochromic shift occurs.

Since the nitro-substituted series clearly plays a special role we carried out electro-optical absorption measurements (EOAM) on the compounds **3c–5c**; a number of the results of these measurements are summarized in Table 2. Assuming that polarizabilities may be neglected with respect to dipole moments, and  $\mu(S_0)$ ,  $\mu(S_1)$ , and the transition moment  $\mu_{01}$  are parallel, EOAM<sup>[10, 11]</sup> gives  $\mu_0$  as well as the terms  $\mu_0(\mu_1 - \mu_0)$  and  $(\mu_1 - \mu_0)^2$ , which are obtained as different regression coefficients from the first and second derivation of  $\epsilon(\tilde{\nu})$  according to the wavenumber  $\tilde{\nu}$ . Both statistically as well as by the EOAM model the first term  $\mu_0(\mu_1 - \mu_0)$  leads to the more reliable values.

As expected, the intensity *I*, the oscillator strength *f*, and the transition moment  $\mu_{01}$  increase with increasing *n*. Surprisingly

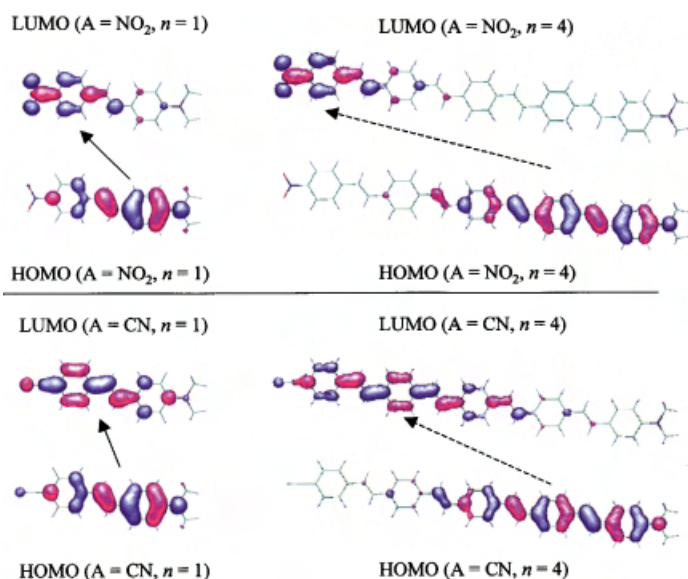


Figure 2. Frontier orbitals of compounds **3b** and **3c**, as well as **6b** and **6c** calculated by the INDO/S method. The arrows illustrate the shift of the electron densities during the HOMO → LUMO transition.



Table 2. Optical and electro-optical data of **3c**, **4c**, and **5c**.<sup>[a]</sup>

| Compound  | <i>n</i> | <i>I</i> [10 <sup>10</sup> cm mol <sup>-1</sup> ] <sup>[b]</sup> | <i>f</i> | $\mu_{01}$ [10 <sup>-30</sup> Cm] | $\mu_0(S_0)$ [10 <sup>-30</sup> Cm] <sup>[c]</sup> | $\mu_1(S_1)$ [10 <sup>-30</sup> Cm] <sup>[c,d]</sup> |
|-----------|----------|------------------------------------------------------------------|----------|-----------------------------------|----------------------------------------------------|------------------------------------------------------|
| <b>3c</b> | 1        | 15.48                                                            | 0.68     | 27.23                             | 29.8                                               | 112.0                                                |
| <b>4c</b> | 2        | 19.70                                                            | 0.86     | 30.30                             | 26.4                                               | 128.8                                                |
| <b>5c</b> | 3        | 31.79                                                            | 1.40     | 38.01                             | 25.3                                               | 108.2                                                |

[a] Measurements in dioxan. [b]  $I = \int \epsilon(\tilde{\nu}) d\tilde{\nu}$ . [c] The statistical regression error is 1–5 % for  $\mu_0$  and 2–6 % for  $\mu_1$ . [d] Determined from  $d\epsilon/d\nu$ ;  $d^2\epsilon/d\nu^2$  gives the less reliable values 106.6, 128.5, and 151.3 Cm for 10<sup>30</sup>  $\mu_1$  with **3c–5c**.

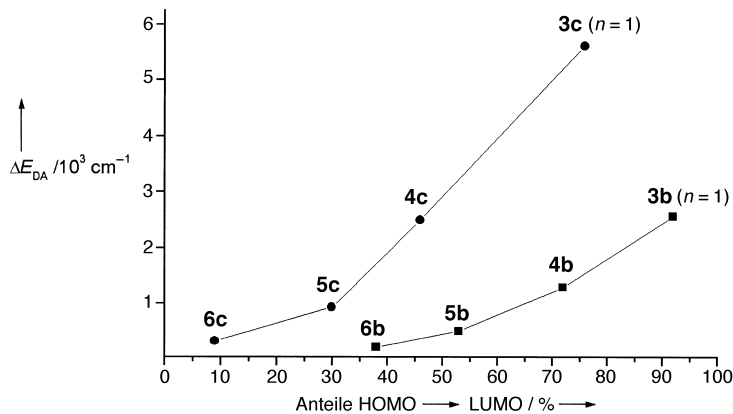


Figure 3. Charge-transfer terms  $\Delta E_{DA}$  in relationship to the HOMO  $\rightarrow$  LUMO fraction calculated by the INDO/S method for the long-wavelength electron transitions in the OPV series **3b–6b** (A = CN) and **3c–6c** (A = NO<sub>2</sub>).

the experimental dipole moment  $\mu_0$  of the ground state  $S_0$  decreases with the increasing distance between donor and acceptor. The dipole moments  $\mu_1$  of the electronically excited state  $S_1$  are significantly higher. Clearly, a simple relationship with the benzenoid and quinoid (zwitterionic) resonance structures formulated in Scheme 1 does not exist. The calculation of resonance parameters known in the literature<sup>[12, 13]</sup> with the values for  $\mu_0(S_0)$ ,  $\mu_1(S_1)$ , and  $\mu_{01}$  given in Table 2 shows that for the compounds **3c–5c** the zwitterionic structure—independent of  $n$ <sup>[14]</sup>—contributes modestly to the ground state at about 10 %. The charge transfer on electronic excitation indeed does increase the dipole moment considerably ( $\Delta\mu = 92.3(\pm 10.1) \times 10^{-30}$  Cm), it has, however, an increasingly smaller influence on the long-wavelength absorption with increasing  $n$  since with increasing distance between donor D and acceptor A at almost constant  $\Delta\mu$ , increasingly less negative charge is transferred to the acceptor part of the molecules. For the conjugated systems with large D–A distances described here the frequently used model of a dominating electrically neutral and a less involved terminal zwitterionic resonance structure is usable for the ground state  $S_0$ . The electronic excited state  $S_1$  does have a significantly higher dipole moment, but the participation of resonance structures never reverses. The simple VB model is not consistent with this.<sup>[15]</sup>

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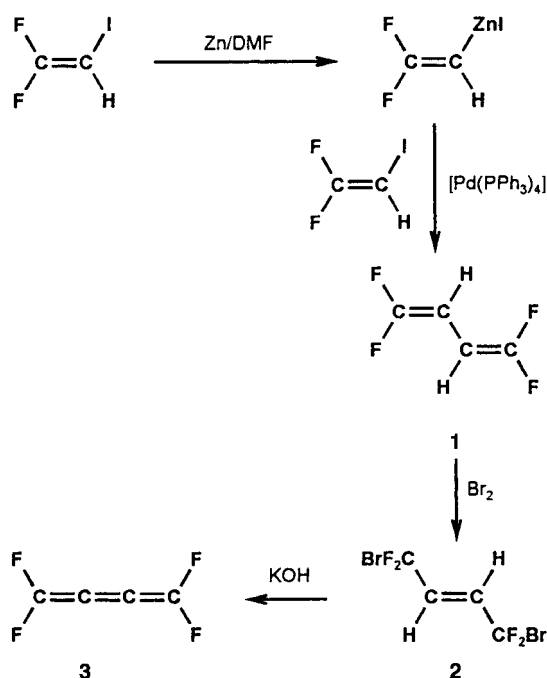
# Crystal Structure Analysis of 1,1,4,4-Tetrafluorobutadiene and Experimental Determination of the Charge Density of 1,1,4,4-Tetrafluorobutatriene\*\*

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1,1,4,4-Tetrafluorobutatriene (**3**) is an extremely reactive molecule that was reported to explode on warming to its boiling point of about  $-5^{\circ}\text{C}$  or even below on contact with air.<sup>[1]</sup> Nevertheless,  $^{19}\text{F}$  NMR,<sup>[1]</sup> IR,<sup>[1,2]</sup> Raman<sup>[2]</sup>, and photoelectron (PE)<sup>[3]</sup> spectra were recorded, although the published multistep synthesis includes some low yield steps<sup>[4,5]</sup> which additionally hinder a detailed study of its reactivity and structure.

Using palladium-catalyzed C–C coupling reactions,<sup>[6]</sup> we were able to develop an effective synthesis of 1,1,4,4-tetrafluorobutadiene (**1**; Scheme 1), which is the key compound in the synthesis of the cumulene **3** and furthermore should possess an interesting versatile chemistry of its own. Reaction of 2,2-difluoroiodoethene with zinc in DMF yields  $\text{F}_2\text{C}=\text{CZnI}$ .<sup>[7]</sup> The subsequent palladium-catalyzed C–C coupling reaction with 2,2-difluoroiodoethene gives good yields of the butadiene **1**; the yields of the other steps are likewise good.<sup>[1]</sup> Owing to the instability of **1** we modified the dehydrobromination reaction: 1,2-Dibromo-1,1,4,4-tetrafluorobut-2-ene (**2**) was passed over potassium hydroxide ( $100^{\circ}\text{C}$ ) under vacuum ( $10^{-3}$  hPa) and the triene **3** was collected in a trap kept at liquid nitrogen temperature. Compound **3** decomposes slowly even at  $-80^{\circ}\text{C}$  forming a colorless solid and is best stored at  $-196^{\circ}\text{C}$ . In the presence of  $\alpha$ -terpinene a viscous oil is formed on warming to ambient temperature.

Owing to the low boiling and melting points of the compounds, crystals had to be grown in situ directly on the diffractometer. Thus **1** and **3** were condensed into glass capillaries (o. d. 0.5 mm) using a glass vacuum line system on cooling with liquid nitrogen; the capillaries were sealed under vacuum, mounted on a goniometer head under low temperatures and brought into a cold gas stream of a diffractometer. Single crystals were grown by slow  $\Phi$  rotation of the capillary



Scheme 1. Synthesis of **3**.

at 157.5 K for **1** and 143.0 K for **3** very close to the melting points of the compounds **1** and **3**, respectively.

Compound **1** crystallizes in the monoclinic space group  $P2_1/n$  with half a molecule in the asymmetric unit and possesses crystallographic  $C_i$  symmetry (Figure 1).<sup>[8]</sup> In the solid state the molecules have the *s-trans* conformation, which is the prevailing one in solution and the gaseous phase despite the

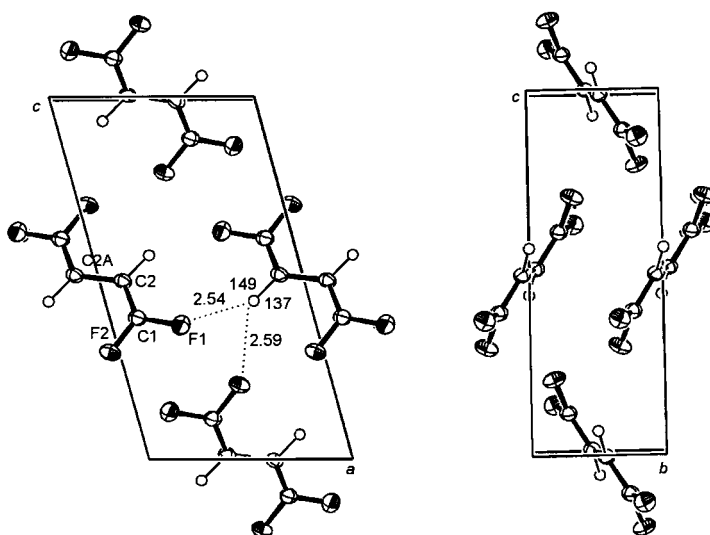


Figure 1. Unit cell of **1** (ORTEP,<sup>[33]</sup> 50% ellipsoids). Left: view along (010); right: view along (100). Short H–F contacts are drawn as dotted lines. Selected bond lengths [Å] and angles [°]: C1–F1 1.323(1), C1–F2 1.319(1), C1–C2 1.321(1), C2–C2A 1.450(2); F1–C1–F2 109.62(8), C1–C2–C2A 122.26(9).

large long-range fluorine coupling constants.<sup>[9]</sup> As expected, the C–C bond lengths alternate and the F1–C1–F2 bond angle is well below  $120^{\circ}$ . The packing of the molecules of **1** in the

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crystal is shown in Figure 1. The molecules are related by short H...F contacts along the *a* axis. A view on the *bc* plane shows the herring-bone arrangement of the molecules.

Compound **3** crystallizes in the monoclinic space group *P*2<sub>1</sub>/*c* (Figure 2),<sup>[8]</sup> and displays a crystal packing very similar to that of ethene<sup>[10]</sup> and tetrafluoroethene<sup>[11]</sup> The common motif again is the typical herring-bone arrangement.<sup>[12]</sup>

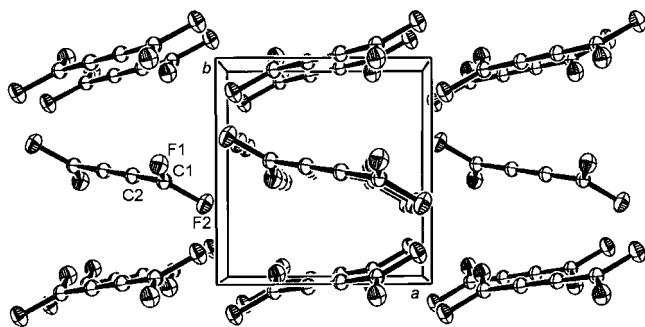


Figure 2. Unit cell of **3** (ORTEP,<sup>[33]</sup> 50% ellipsoids), view along (001).

The charge density  $\rho(\mathbf{r})$  can be deduced theoretically from ab initio calculations at high level and experimentally from high-resolution X-ray diffraction data at low temperature.<sup>[13]</sup> The topological analysis of the charge density based on the theory of atoms in molecules (AIM) developed by Bader,<sup>[14, 15]</sup> allows a quantitative description of bonds and nonbonding interactions. Partitioning of a structure into submolecular regions (atoms or functional groups) provides a quantitative description of atomic properties such as atomic volumes and atomic charges. Since simple fluorinated alkenes are gaseous at ambient temperature, only a few crystal structure determinations or even charge density determinations have been carried out so far.<sup>[16–19]</sup> In pioneering work, Irngartiner et al. determined the charge density of cumulenes with bulky substituents.<sup>[20]</sup>

High resolution X-ray data were collected for **3**<sup>[8]</sup> and were used for a multipole refinement based on the Hansen–Coppens formalism<sup>[21]</sup> and a topological analysis using the program package XD was performed.<sup>[22]</sup>

The experimental static deformation densities for two perpendicular planes of **3** are represented in Figure 3a and 3b, from which the perpendicular  $\pi$  systems of the cumulene are clearly evident. In the molecular plane the electron density of the central double bond appears to be more elongated perpendicular to the bond axis than in the neighboring bonds; the opposite is seen in the plane perpendicular to the molecular plane. The charge density in the outer double bonds is shifted towards the fluorine substituents.

The results of the topological analysis of  $\rho(\mathbf{r})$  at the bond critical points (BCPs; BCP at the location  $\mathbf{r}_b$  is defined by  $\nabla\rho(\mathbf{r}_b)=0$ ) enable a quantitative description of the bonds. The experimental results are found to be in good agreement with the theoretical ones (Table 1) except for the Laplacian  $-\nabla^2\rho(\mathbf{r}_b)$  in the polar C–F bonds. These differences for polar

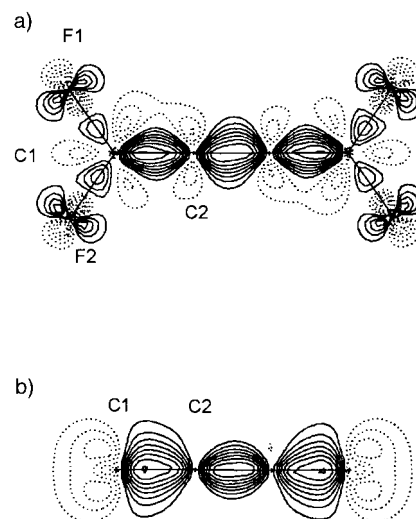


Figure 3. Experimental static deformation density in the molecular plane (a) and perpendicular to the molecular plane and parallel to the molecular axis (b). The contour intervals are at 0.1 e Å<sup>−3</sup>, negative lines are dotted.

Table 1. Topological parameters at the BCPs of **3** (experiment/theory).<sup>[a]</sup>

| Bond   | Bond length<br>[Å] | $d_1$<br>[Å] <sup>[b]</sup> | $\rho(\mathbf{r})$<br>[e Å <sup>−3</sup> ] | $-\nabla^2\rho(\mathbf{r})$<br>[e Å <sup>−5</sup> ] | $\epsilon$ |
|--------|--------------------|-----------------------------|--------------------------------------------|-----------------------------------------------------|------------|
| C1–F1  | 1.3198(3)/1.3189   | 0.518/0.444                 | 2.13(1)/1.97                               | 25.0(1)/3.05                                        | 0.13/0.23  |
| C1–F2  | 1.3222(3)/1.3189   | 0.533/0.444                 | 2.20(1)/1.97                               | 24.3(1)/3.05                                        | 0.08/0.23  |
| C1–C2  | 1.3162(3)/1.3089   | 0.654/0.680                 | 2.43(2)/2.44                               | 24.0(1)/27.39                                       | 0.32/0.50  |
| C2–C2' | 1.2679(5)/1.2584   | 0.634/0.629                 | 2.63(2)/2.57                               | 30.5(1)/29.12                                       | 0.14/0.20  |

[a] Geometry optimization using B3LYP/6–311 + G(3df).<sup>[31]</sup> [b]  $d_1$  the distance of the first atom of a bond to the BCP.

bonds have been observed before.<sup>[16, 18, 23, 24]</sup> According to Coppens et al.<sup>[25]</sup> the main origin of these discrepancies is attributed to the nature of the radial functions in the experimental multipole model.

The topological parameters of the cumulated double bonds C1–C2 and C2–C2' (the third double bond C2'–C1' is equivalent to C1–C2 by crystallographic symmetry) reveal more interesting aspects. At the BCP of the shorter central bond the charge density and the negative Laplacian ( $\rho(\mathbf{r}_b) = 2.63$  e Å<sup>−3</sup> and  $-\nabla^2\rho(\mathbf{r}_b) = 30.5$  e Å<sup>−5</sup>) are significantly larger than for the neighboring longer bonds ( $\rho(\mathbf{r}_b) = 2.43$  e Å<sup>−3</sup> and  $-\nabla^2\rho(\mathbf{r}_b) = 24.0$  e Å<sup>−5</sup>). Thereby the charge density is not only concentrated on the fluorine atoms but also on the inner double bond. These experimental results agree very well with those of the theoretical topological analysis (Table 1).<sup>[14]</sup> There is a striking difference in the ellipticities  $\epsilon$ <sup>[26]</sup> of the outer double bond ( $\epsilon = 0.32$ ) and the inner double bond ( $\epsilon = 0.14$ ). These results confirm the idea of sp-hybridization for the inner carbon atoms in cumulenes. The shorter bond length, the higher charge density, and the smaller ellipticity are attributed to the higher s-character for the central bond.

The partitioning of **3** into submolecular regions according to Bader<sup>[14, 15]</sup> can be deduced from the topology of  $\rho(\mathbf{r})$ . Atomic regions are limited by zero flux surfaces (ZFS) as boundaries. A ZFS is defined by Equation (1) ( $\mathbf{n}$  = unit vector perpendicular to the surface).

$$\nabla\rho(\mathbf{r})\mathbf{n}(\mathbf{r}) = 0 \text{ at every point of the surface} \quad (1)$$

The nuclear positions are local maxima of the charge density and thereby attractors of the gradient vector field  $\nabla\rho(\mathbf{r})$ . Figure 4 presents the gradient vector field  $\nabla\rho(\mathbf{r})$  (experiment and theory) in the molecular plane. The atomic volume can be calculated from the ZFS. The atomic charges

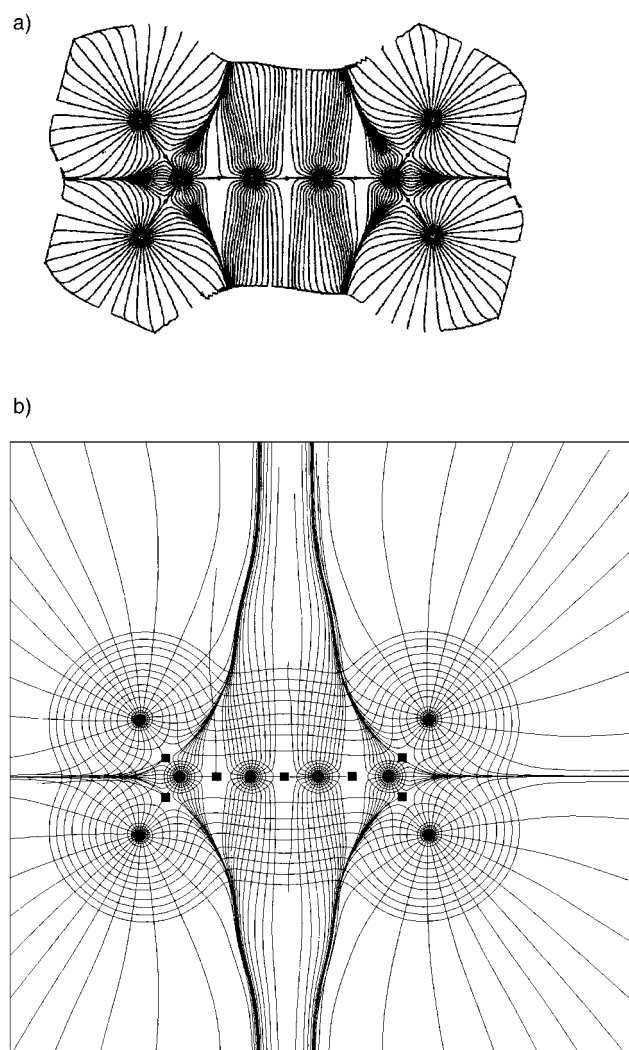


Figure 4. The gradient vector field  $\nabla\rho(\mathbf{r})$  in the molecular plane of **3**. a) From experimental data; b) from ab initio calculations with isolines of  $\nabla\rho(\mathbf{r})$ . Circles: atomic positions; squares: bond critical points.

were obtained by integration of  $\rho(\mathbf{r})$  over these volumes. The computation of atomic volumes and charges based on experimental data was performed by the use of the program TOPXD.<sup>[27, 28]</sup> The computation of these parameters by theory was performed with the program MORPHY 98.<sup>[29]</sup> Both, the experimental and theoretical results are in very good agreement (Table 2). The sum of the atomic volumes, derived by both methods, are equal to the cell volume<sup>[8]</sup> within an error of only 0.1 %. The high positive charge of +1.13 (experiment) and +1.267 (theory) at C1 gives an idea of the high reactivity (favored site for nucleophilic attack).

The electrostatic potential was calculated by using the method of Su and Coppens<sup>[30]</sup> on the basis of experimental data. This calculation considers a molecule of **3** extracted from

Table 2. AIM volumes and charges of **3** (experiment/theory).<sup>[a]</sup>

| Atom | Charge [e]       | Volume [ $\text{\AA}^3$ ] |
|------|------------------|---------------------------|
| F1   | − 0.593/ − 0.636 | 15.58/15.94               |
| F2   | − 0.591/ − 0.636 | 15.96/15.95               |
| C1   | + 1.130/ + 1.267 | 7.86/7.47                 |
| C2   | + 0.053/ + 0.002 | 15.51/15.56               |

[a] Geometry optimization using B3LYP/6−311 + G(3df).<sup>[31]</sup>

the crystal but still containing the polarization effects induced by intermolecular interactions. Figure 5 displays an isosurface representation of the electrostatic potential. As expected, the negative potential is concentrated around the fluorine atoms and the positive potential along the molecular axis; the electrostatic potential corresponds to the crystal packing in a kind of a herring-bone motif.

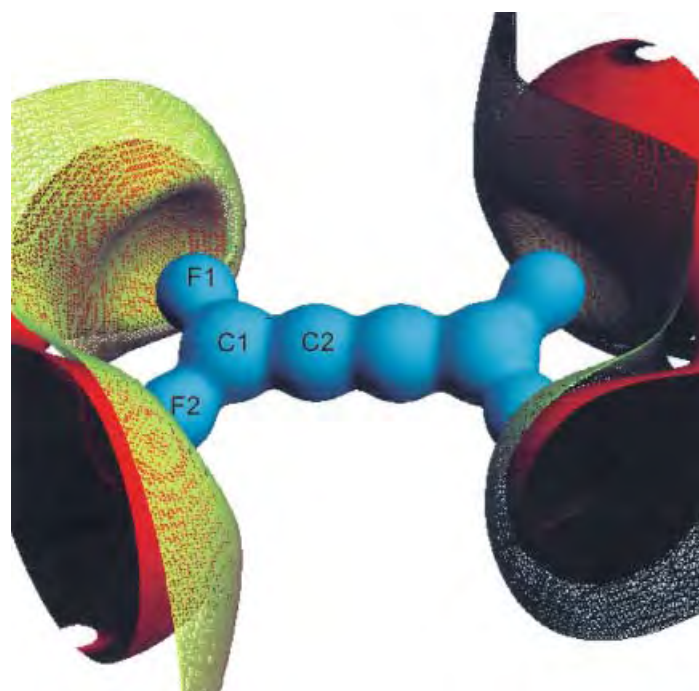


Figure 5. Three-dimensional distribution of the electrostatic potential based on experimental data for **3**; three isopotential surfaces are shown: blue 0.50, red −0.03, and net 0.00  $\text{e \AA}^{-1}$ .

## Experimental Section

**1:** 1-Iodo-2,2-difluoroethene (13 g, 68.45 mmol) was added dropwise to activated zinc powder (8 g) in DMF (50 mL) at 60 °C and stirred for 1 h at 60 °C. The solution of the zinc reagent was added to  $[\text{Pd}(\text{PPh}_3)_4]$  (2 g, 1.7 mmol, 2.5 mol %) in a second flask. After the mixture had been warmed to 75 °C, 1-iodo-2,2-difluoroethene (13 g, 68.45 mmol) was added slowly. The temperature of the reflux condenser was adjusted to 5 °C during the addition and to 20 °C after the addition. The reaction temperature was maintained at 75 °C for an additional 4 h. The product was collected as a colorless liquid in a trap kept at −78 °C. Purification by fractional condensation under vacuum ( $10^{-3}$  hPa) yielded **1** (5.7 g, 45 mmol) in the trap kept at −120 °C. IR (gas):  $\tilde{\nu}$  = 3122 vw, 1740 sh, 1715 vs, 1321 s, 1172 m 1140 w, 949 m, 922 s, 826 w 739 vw, 548 vw  $\text{cm}^{-1}$  (in agreement with literature data<sup>[32]</sup>); the  $^{19}\text{F}$  and  $^1\text{H}$  NMR spectra exhibit the pattern of an AA'BB'XX' spin system which was already analyzed earlier.<sup>[9]</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 4.52 (m);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = −86.77 (m), −88.09 (m);  $^{13}\text{C}\{^1\text{H}\}$  NMR:  $\delta$  = 72.3 (m), 155.6 (m).

**2:** Compound **1** (5.4 g, 42 mmol) was condensed onto Br<sub>2</sub> (6.7 g, 42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) in a 100 mL glass flask. The reaction mixture was stirred for 5 h at ambient temperature. Fractional condensation under vacuum yielded **2** (6.2 g, 51.5 %) as a pale yellow liquid in the trap kept at –60 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 6.33 (m); <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = –50.3 (m); <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ = 114.2 (t, <sup>1</sup>J(<sup>19</sup>F, <sup>13</sup>C) = 301 Hz; CF<sub>2</sub>), 129.3 (<sup>2</sup>J(<sup>19</sup>F, <sup>13</sup>C) = 27 Hz, <sup>3</sup>J(<sup>19</sup>F, <sup>13</sup>C) = 7 Hz; CH).

**3:** Compound **2** (1 g, 3.5 mmol) was passed over KOH which was filled into a U-shaped tube heated to 90 °C by evaporation under vacuum (10<sup>–3</sup> hPa). The volatile materials were collected in traps kept at –78 °C (starting material **2**) and –196 °C (**3**). This was repeated until practically all starting material **2** had reacted. A yield of 43 % was determined by p/V/T measurement; m.p. –130 °C; <sup>19</sup>F NMR (CD<sub>2</sub>Cl<sub>2</sub>, 193 K): δ = –96.1 (s); <sup>13</sup>C {<sup>19</sup>F} NMR (CD<sub>2</sub>Cl<sub>2</sub>, 193 K): δ = 147.8, 158.9; IR (gas): ν̄ = 1732, 1281, 973, 939, 536 cm<sup>–1</sup>; Raman (250 mW, 193 K): ν̄ = 2137 m, 2103 vw, 1374 vw, 984 w, 951 w, 788 w, 724 m, 475 vs, 374 w, 351 m, 185 m cm<sup>–1</sup>.

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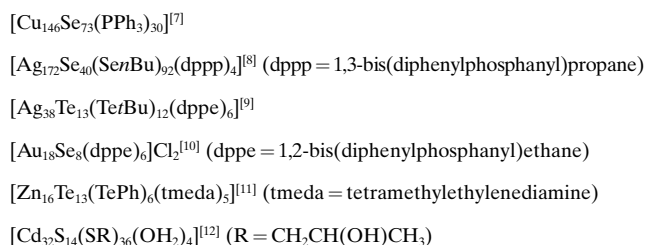
**Synthesis and Structures of Silver–Selenide Cluster Complexes [Ag<sub>4</sub>(SeiPr)<sub>4</sub>(dppm)<sub>2</sub>], [Ag<sub>8</sub>(SeEt)<sub>8</sub>(dppp)]<sub>∞</sub>, [Ag<sub>28</sub>Se<sub>6</sub>(SenBu)<sub>16</sub>(dppp)<sub>4</sub>], and [Ag<sub>124</sub>Se<sub>57</sub>(SePrBu<sub>2</sub>)<sub>4</sub>Cl<sub>6</sub>(*t*Bu<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PrBu<sub>2</sub>)<sub>12</sub>]<sup>\*\*</sup>**

Dieter Fenske\* and Timo Langetepe

*Dedicated to Professor Jochen Strähle on the occasion of his 65th birthday*

The specific synthesis of nanometer-sized clusters and colloids is of particular interest because of the electronic and optical properties of this type of substances.<sup>[1, 2]</sup> Colloids as well as ligand-stabilized sections of metals<sup>[3]</sup> and semiconductor clusters<sup>[4]</sup> have been intensively studied. As result of the quantum size effect, the clusters show a dependence of the band gap on the particle size. In the last few years, we have been working on the synthesis of cluster complexes whose core is formed, for example, by transition metal chalcogenides.<sup>[5]</sup> This core is protected by a shell of ligands from self-aggregation, which would lead to the thermodynamically stable binary phase.<sup>[6]</sup>

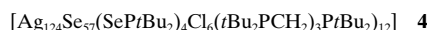
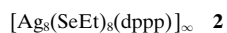
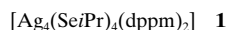
One approach to the preparation of metal chalcogen bridged cluster complexes is the reaction of transition metal salts, or their phosphane complexes with silylated chalcogenide compounds of the general type E(SiMe<sub>3</sub>)<sub>2</sub> or RESiMe<sub>3</sub> (R = alkyl or aryl; E = S, Se, Te). The driving force of the reaction is the formation of XSiMe<sub>3</sub> (X = Cl, Br, OAc, etc). In this way we have prepared and characterized a large number of cluster compounds, examples of which are given in Scheme 1.



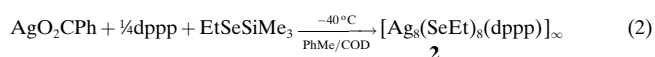
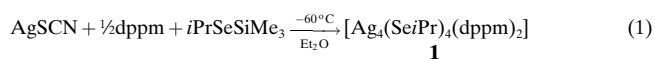
Scheme 1.

These compounds are usually obtained in a high yield. It shows that the used reactants and the reaction conditions are crucial for the observed composition of the isolated cluster complexes. However, several species are probably present in an equilibrium existing in the reaction mixture, from which that with the lowest solubility will crystallize. Therefore it is

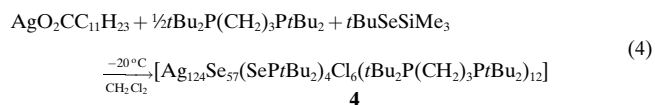
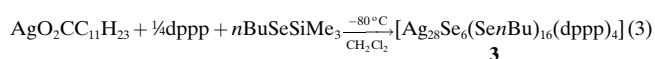
not surprising, that even a slight change in the reaction conditions may cause the formation of novel, yet unknown cluster structures. Herein, we describe the synthesis and crystal structures of **1–4**.



Reaction of silver thiocyanate, bis(diphenylphosphanyl)methane (dppm), and *i*PrSeSiMe<sub>3</sub> in diethyl ether gave the complex **1** [Eq. (1)]. The analogous reaction with silver benzoate gave the same reaction product, however, in lower yields. Reaction of silver benzoate, dppp, and EtSeSiMe<sub>3</sub> in a mixture of 1,4-cyclooctadiene (COD) and toluene [Eq. (2)] led to the formation of an orange solution, from which small yellow crystals of **2** have been isolated.



The reaction of silver laureate, dppp, and *n*BuSeSiMe<sub>3</sub> in dichloromethane at –20 °C, led to the formation of small red crystals of **3** [Eq. (3)]. These crystals are very sensitive. They already decompose at temperatures above –10 °C into unknown substances. Evidently, the reaction conditions, especially the solvent, play an important role, since the reaction of the same starting compounds in a mixture of toluene and chloroform gave the largest known silver cluster [Ag<sub>172</sub>Se<sub>40</sub>(SenBu)<sub>92</sub>(dppp)<sub>4</sub>].<sup>[8]</sup> Reaction of silver laureate with 1,3-bis(di-*tert*-butylphosphanyl)propane (*t*Bu<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PrBu<sub>2</sub>) and *t*BuSeSiMe<sub>3</sub> in dichloromethane at –20 °C, small black crystals of **4** were formed [Eq. (4)].



The molecular structures of **1–4** were determined by single-crystal X-ray structural analysis.<sup>[13]</sup>

Complex **1** crystallizes in the form of yellow cubes in the acentric space group *P*2<sub>1</sub> with two formula units in the asymmetric unit. The molecular structure of one of the two independent molecules of **1** is shown in Figure 1 a. The bond lengths and angles of the two independent clusters are identical, within standard deviation. The complex is based on an Ag<sub>4</sub> tetrahedron, whose four edges are bridged by selenium atoms of the SeiPr ligands. Ag–Ag distances range from 305.8(2) to 335.1(2) pm, indicating nonbonding metal–metal interactions. Assuming a formal charge of –1 for the selenolate ligands, all silver atoms are charged +1. The Ag–

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[\*\*] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 195) and the Fonds der Chemischen Industrie. dppm = bis(diphenylphosphanyl)methane, dppp = 1,3-bis-(diphenylphosphanyl)propane.



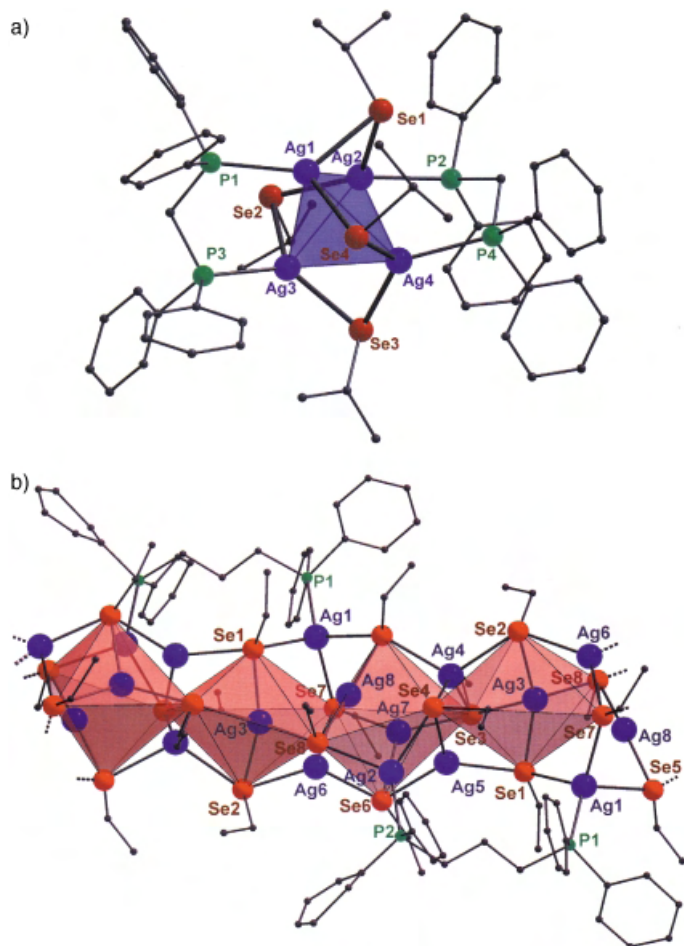


Figure 1. a) Molecular structure of **1** in the crystal (color code: Ag: blue, Se: red, P: green, C: gray). Selected distances [pm] and angles [°]: Ag1–Ag2 335.1(2), Ag3–Ag4 311.3(2), Ag1–Se4 264.5(2), Ag3–Se2 265.4(2), Ag4–Se3 263.9(3), Ag4–Se4 251.7(3), Ag1–P1 250.2(5); Ag2–Ag1–Ag3 56.1(1), Ag2–Ag1–Ag4 58.1(1), Ag3–Ag1–Ag4 59.9(1), Ag2–Se2–Ag3 71.2(1). b) Section of the structure of the polymeric compound **2** in the crystal (color code as in a). The linked  $\text{Se}_6$  octahedrons in the polymeric chain, are represented as polyhedrons. Selected distances [pm] and angles [°]: Ag3–Ag4 291.1(3), Ag6–Ag8 332.5(4), Ag1–Se1 268.0(2), Ag1–Se5 274.7(7), Ag1–Se7 260.8(4), Ag3–Se1 262.6(3), Ag3–Se2 280.3(2), Ag3–Se3 284.7(3), Ag3–Se8 273.0(3), Ag4–Se2 280.3(3), Ag6–Se2 255.9(3), Ag8–Se5 250.9(4), Ag8–Se8 252.2(4), Ag1–P1 240.6(6), Ag2–P2 241.3(6); P2–Ag2–Se4 137.8(2), P2–Ag2–Se8 122.7(2), Se4–Ag2–Se8 98.0(2), Se1–Ag3–Se3 87.4(1), Se3–Ag4–Se4 129.5(2), Se1–Ag5–Se4 107.9(1), Se1–Ag5–Se6 135.9(2), Se4–Ag5–Se6 115.4(1), Se5–Ag8–Se8 164.2(2), Ag4–Se3–Ag7 68.5(1), Ag2–Se8–Ag3 151.8(2).

Se–Ag angles at the selenium atoms Se1–Se4 are 71.2(1)–80.6(1)°. The Ag–Se bond lengths are 251.7(3)–265.4(2) pm, which is a typical range for  $\mu_2$ -bridging selenolate ligands between silver atoms. All silver atoms show distorted trigonal-planar coordination geometry (sum of angles: 352.6–358.4°), coordinated to two selenium atoms and one phosphorus atom of a dppm ligand (Ag–P distances: 242.0(4)–250.5(4) pm).

Complex **2** (Figure 1b) crystallizes in the monoclinic space group  $C2/c$  with eight formula units per unit cell. Complex **2** is a polymeric compound, formed by a strand of distorted edge-sharing  $\text{Se}_6$  octahedrons (Se–Se distances: 378.6(4)–553.9(5) pm). All eight  $(\text{SeEt})^-$  ligands act as  $\mu_3$  bridges

between silver atoms. The Ag–Se bond lengths range between 250.9(4) and 284.7(3) pm. All silver atoms in **2** show different coordination modes. Ag1 is surrounded tetrahedrally by three selenium atoms (Se1, Se5, Se7) that form the face of an octahedron, and one phosphorus atom (P1) of a dppp ligand. Ag2 binds two corners of the  $\text{Se}_6$  octahedron (Se4, Se8) and the other phosphorus atom of the dppp ligand (P2), and thus shows a distorted trigonal-planar coordination geometry (sum of angles: 358.6°). Ag3 and Ag4 are surrounded by four selenium atoms leading to the formation of a distorted tetrahedron. While Ag4 is located between two neighboring  $\text{Se}_3$  faces (Se2, Se3, Se4; Se3, Se4, Se5), Ag3 lies within a  $\text{Se}_6$  octahedron and binds to Se1, Se2, Se3, and Se8. The Se–Ag–Se angles range between 87.4(1) and 129.5(2)°. Three silver atoms show a trigonal-planar coordination geometry, each binding to three selenium atoms (sum of angles: 359.2° (Ag5), 360.0° (Ag6), and 354.4° (Ag7)). Ag5 and Ag6 are coordinated to two selenium atoms that form the top of the  $\text{Se}_6$  octahedrons (Se1, Se6 and Se2, Se6, respectively) and one more selenium atom each of an equatorial plane (Se4 and Se7, respectively). Silver atom Ag7, however, centers an  $\text{Se}_3$  octahedral face (Se3, Se6, Se7). Ag8 has the smallest coordination number of all silver atoms. It is bound linearly to two selenium atoms above an edge of an octahedron (Se5 and Se8, angle Se5–Ag8–Se8: 164.2(2)°). The Ag–Ag distances of 291.1(3) to 332.5(4) pm do not indicate binding interactions. The low steric protection of the Ag–Se core of the polymer is noticeable.

Complex **3** crystallizes in the monoclinic space group  $C2/c$  and contains four formula units and 20 molecules of dichloromethane per unit cell. The molecular structure of **3** ( $\bar{1}$  symmetry) is shown in Figure 2. Six of the 22 selenium atoms are “naked” selenido ligands (Se1, Se2, Se3, and symmetry-equivalent positions) and form a distorted octahedron. The edge lengths of this polyhedron (463.0(2)–531.1(2) pm) indicate these are nonbonding interactions. The 16 selenium atoms of the  $\text{SenBu}$  groups form a layer-type substructure together with the selenido ligands, in which Se3, Se4, Se6, Se7, Se8, Se9, and Se11 as well as Se1, Se2, Se5, and Se10 and symmetry equivalents form the layers. The silver atoms show different coordination modes. Four silver atoms, Ag5, Ag6, and symmetry-equivalent sites are surrounded by selenium atoms, forming distorted tetrahedral angles (92.8(1)–128.1(1)°). 14 further silver atoms (Ag7, Ag8, Ag9, Ag10, Ag11, Ag12, Ag13, and symmetry equivalents) are trigonal-planarly coordinated to selenium atoms (sum of angles: 356.6–359.9°). However, some of the angles deviate clearly from 120° (93.4(1)–165.4(1)°). Ag14/Ag14' bind to two selenium atoms Se2/Se3' or Se2'/Se3, respectively. The remaining eight silver atoms (Ag1, Ag2, Ag3, Ag4 and symmetry-equivalent positions) are each coordinated by one phosphorus atom and selenium atoms of the  $\text{SenBu}$  ligands and show tetrahedral (Ag1) or trigonal-planar coordination geometry (Ag2, Ag3, Ag4).

Complex **4** crystallizes in the monoclinic space group  $P2_1/c$  with four molecules per unit cell. The spherical cluster molecule (Figure 3) contains 124 silver and 61 selenium atoms and has a size of approximately 3 nm. Additionally six chlorine atoms are found as ligands. Four of them (Cl3–Cl6)

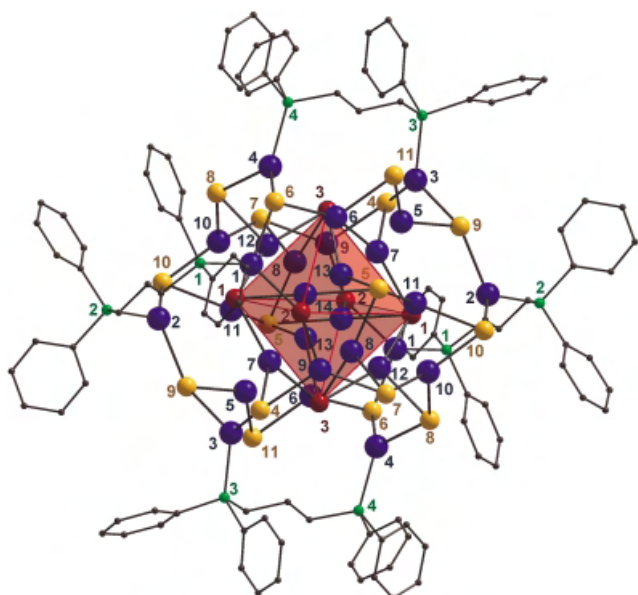


Figure 2. Molecular structure of **3** in the crystal (*n*-butyl groups are omitted for clarity; color code: Ag: blue, Se (selenide ligands): dark red, Se (selenato ligands): orange, P: green, C: gray). The atom number is given and the corresponding atom type can be deduced from the color. Selected distances [pm] and angles [°]: Ag1–Ag5 286.5(1), Ag3–Ag5 299.6(1), Ag6–Ag12 321.6(2), Ag6–Se1 256.4(2), Ag7–Se6 257.9(2), Ag9–Se5 261.5(2), Ag9–Se6 310.8(2), Ag11–Se10 287.7(2), Ag1–P1 243.3(3), Ag13–P4 241.9(2); P1–Ag1–Se2 107.3(1), P3–Ag2–Se4 123.9(1), P3–Ag2–Se9 116.0(1), Se4–Ag2–Se9 116.3(1), Se6–Ag6–Se8 98.5(1), Se6–Ag7–Se8 127.1(1), Se6–Ag8–Se7 93.4(1), Se7–Ag8–Se8 101.1(1), Se3–Ag12–Se8 154.4(1), Ag6–Se1–Ag13 76.0(1), Ag1–Se3–Ag11 162.0(1), Ag3–Se3–Ag12 111.5(1), Ag6–Se6–Ag9 56.3(1).

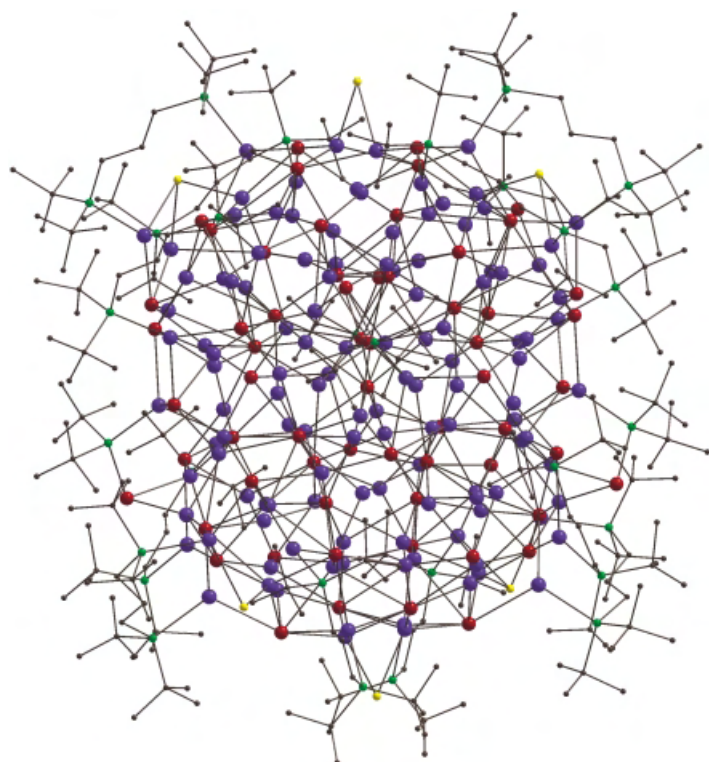


Figure 3. Molecular structure of **4** in the crystal (color code: Ag: blue, Se: dark red, P: green, Cl: yellow, C: gray)

are  $\mu_3$ -bridging on the cluster surface with Ag–Cl bond lengths of between 257.4(4) and 290.3(8) pm. Two further chlorine atoms (Cl1, Cl2) only bridge two silver atoms with Ag–Cl distances of 256.6(9) to 278.3(9) pm (Figure 4). The

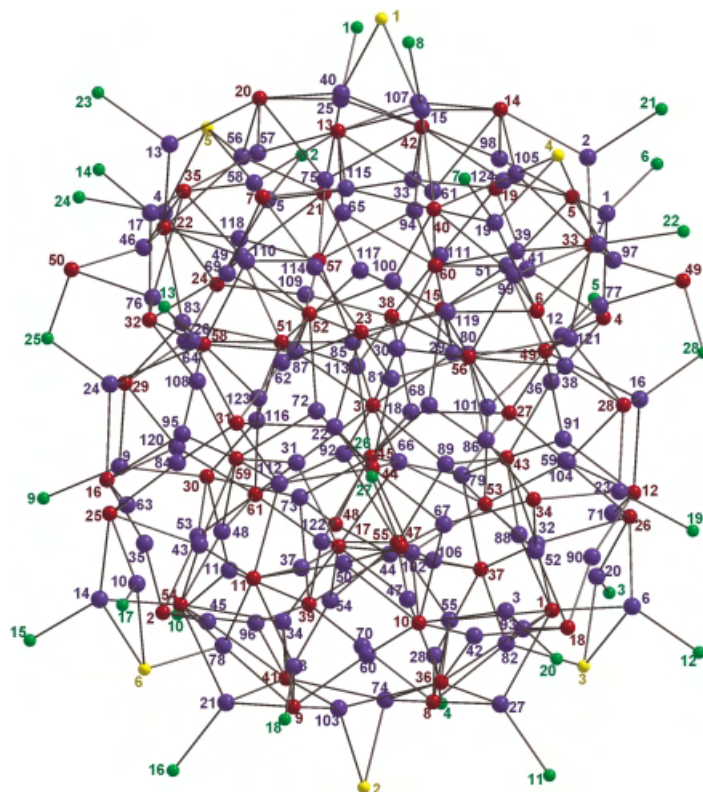


Figure 4. Cluster core of **4** in same orientation as in Figure 3 (with same color code), without carbon and hydrogen atoms. Selected distances [pm] and angles [°]: Ag41–Ag51 337.9(4), Ag74–Ag103 271.9(4), Ag85–Se3 270.1(3), Ag92–Se3 277.2(3), Ag111–Se38 249.1(4), Ag121–Se56 310.1(4), Ag5–Cl5 290.3(8), Ag40–Cl1 256.6(9), Ag74–Cl2 278.3(9), Ag78–Cl6 257.4(8), Ag2–P21 250.0(11), Ag18–P26 245.8(7), Ag21–P16 244.2(8), Ag24–P25 242.6(8), Se48–P26 224.0(8), Se50–P25 227.2(8); Ag27–Se8–Ag55 54.8(1), Ag89–Se3–Ag87 175.9(2), Se17–Ag37–Se11 170.1(2), Se5–Ag51–Se15 136.3(2), Se48–Ag73–Se39 82.5(8), Se14–Ag98–Se5 128.0(2), P20–Ag3–Se10 132.7(2), P24–Ag4–Se24 129.4(2), P27–Ag22–Se44 104.0(2), P27–Se47–Ag67 103.0(2), P28–Se49–Ag77 98.1(2), Ag24–P25–Se50 115.3(3), Ag18–P26–Se48 116.1(3), Cl5–Ag4–P24 107.7(3), Cl5–Ag4–Se24 118.1(2), Cl1–Ag40–Se20 127.7(2), Cl1–Ag40–Se42 95.7(2), Ag40–Cl1–Ag107 64.1(2), Ag74–Cl2–Ag103 60.2(2), Ag20–Cl3–Ag82 95.2(2).

Ag–Cl–Ag angles lie between 60.2(2) and 95.2(2)°. All chloro ligands probably come from the solvent (dichloromethane).

A more exact description of the structure of **4** is exceptionally difficult since there is no similarity to the cluster structures known until now. The most significant structural feature is a slightly twisted Frank–Kasper polyhedron surrounding the central atom Se3. Its 16 selenium atoms (Se15, Se17, Se43, Se44, Se45, Se46, Se51, Se52, Se53, Se55, Se56, Se57, Se58, Se59, Se60, Se61) show distances of 493.2–536.0 pm to Se3 (Figure 5). The Se–Se distances within this polyhedron range between 434.9 and 506.0 pm. The next shell is formed by the 44 selenium atoms of the remaining 40 selenido and four (SePrBu<sub>2</sub>)<sup>–</sup> ligands. They are placed at distances of 770.8 to 938.7 pm around Se3 and form a strongly



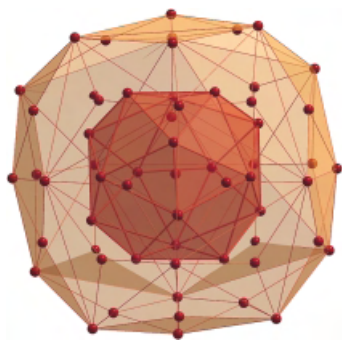


Figure 5. Selenium substructure of **4**. The central atom Se3 is surrounded by the Se<sub>16</sub> Frank – Kasper polyhedron (red) in the first coordination sphere and by the Se<sub>44</sub> polyhedron in the second coordination sphere (orange).

distorted deltahedron of 84  $\Delta_3$  faces (Se–Se distances: 380.1 to 599.4 pm) that can be described on the basis of a growth of the Se<sub>16</sub> Frank–Kasper polyhedron.<sup>[14]</sup> Twelve of the 28 tetrahedral holes of the Se<sub>16</sub> deltahedron centered about Se3 are occupied by silver atoms, that, however, show a distorted coordination. A further 80 silver atoms are situated between the Se<sub>16</sub> polyhedron and the Se<sub>44</sub> polyhedron, and display different coordination modes. Apart from the occupation of tetrahedral holes, silver atoms show the coordination number two or three. Finally, 32 silver atoms are located on the cluster surface, and either obtain a distorted tetrahedral or trigonal-planar coordination.

The selenido ligands in **4** act as  $\mu_3$ ,  $\mu_4$ ,  $\mu_5$ ,  $\mu_6$ ,  $\mu_7$ , or  $\mu_8$  bridges between the silver atoms. All Ag–Se bond lengths lie in the range between 249.1(4) and 310.1(3) pm and the angles Ag–Se–Ag range between 54.8(1) and 175.9(1)°. If we assume 57 Se<sup>2–</sup>, six Cl<sup>1–</sup>, and four (SePtBu<sub>2</sub>)<sup>–</sup> ligands are present, all silver atoms are formally charged 1+. Consequently the nonbonding Ag–Ag distances range between 271.9(4) and 337.9(4) pm. The (SePtBu<sub>2</sub>)<sup>–</sup> ligands coordinated on the cluster surface are each bound to two silver atoms through the selenium atoms and to another silver atom through the phosphorus atoms. Evidently, the formation of this ion might be the result of a decomposition reaction.

No characteristic details of the Ag<sub>2</sub>Se phases are visible in the structure of **4**.<sup>[15]</sup> This is astonishing, since we have previously shown that the formation of Ag<sub>2</sub>Se substructures in molecular cluster complexes depends on the size of the cluster.<sup>[8]</sup> For example, a transition to the structure of  $\alpha$ -Ag<sub>2</sub>Se is found in selenido- and selenolato-bridged silver clusters, depending on the number of silver atoms. In smaller clusters such as [Ag<sub>30</sub>Se<sub>8</sub>(Se<sup>–</sup>Bu)<sub>14</sub>(PnPr<sub>3</sub>)<sub>8</sub>] and [Ag<sub>90</sub>Se<sub>38</sub>(Se<sup>–</sup>Bu)<sub>14</sub>(PEt<sub>3</sub>)<sub>22</sub>] no relationship to the structure of binary Ag<sub>2</sub>Se is observed. However, for the compounds [Ag<sub>112</sub>Se<sub>32</sub>(SenBu)<sub>48</sub>(PtBu<sub>3</sub>)<sub>12</sub>], [Ag<sub>114</sub>Se<sub>34</sub>(SenBu)<sub>46</sub>(PtBu<sub>3</sub>)<sub>14</sub>], and [Ag<sub>172</sub>Se<sub>40</sub>(SenBu)<sub>92</sub>(dppp)<sub>4</sub>] the structural transition becomes clear. Which other factors influence the point at which this structural transition occurs are currently under investigation.

## Experimental Section

**1:** A suspension of AgSCN (1.21 mmol, 200 mg) and Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PPh<sub>2</sub> (0.60 mmol, 230 mg) in diethyl ether (10 mL) was treated with *i*PrSeSiMe<sub>3</sub>

(1.21 mmol, 0.25 mL) at –60 °C. The resulting yellow solution was stirred for two hours and stored for three weeks at –20 °C. After another week at room temperature, small yellow crystals of **1** grew together with a microcrystalline solid (yield 45 %).

**2:** A suspension of AgO<sub>2</sub>CPh (1.14 mmol, 260 mg) and Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PPh<sub>2</sub> (0.28 mmol, 120 mg) in toluene (10 mL) and COD (0.14 mL) was treated with EtSeSiMe<sub>3</sub> (1.14 mmol, 0.22 mL) at –40 °C. After the mixture had been stirred for two hours, the orange solution was warmed up to room temperature. After one week, a brown precipitate was formed. It was separated, and the solution was again stored for one week. Within this time, small yellow needles of **2** crystallized in low yield (30 %).

**3:** A suspension of AgO<sub>2</sub>CC<sub>11</sub>H<sub>23</sub> (1.04 mmol, 320 mg) and Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>PPh<sub>2</sub> (0.26 mmol, 110 mg) in dichloromethane (10 mL) was treated with *n*BuSeSiMe<sub>3</sub> (1.04 mmol, 0.23 mL) at –80 °C. The red solution was slowly warmed up to –20 °C over three days and stored at this temperature. Red needles of **3** appeared in 45 % yield.

**4:** A suspension of AgO<sub>2</sub>CC<sub>11</sub>H<sub>23</sub> (0.91 mmol, 280 mg) and *t*Bu<sub>2</sub>P(CH<sub>2</sub>)<sub>3</sub>Pr-Bu<sub>2</sub> (0.46 mmol, 310 mg) in dichloromethane (10 mL) was treated with *t*BuSeSiMe<sub>3</sub> (0.91 mmol, 0.25 mL) at –20 °C. The red solution was then stirred for two hours and stored for three weeks at –20 °C. After another week at room temperature, small black crystals of **4** grew together with a microcrystalline solid in a low yield (20 %).

The Ag, P, C, H analysis of **1–4** correspond to the stated formulas.

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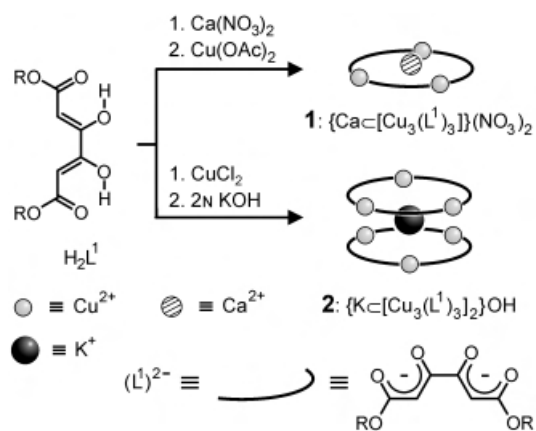
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## Hybrid Metallacoronates or One-Dimensional Oxo-Bridged Metal Strings by Self-Assembly—Coordination Number Controlled Product Formation\*\*

Rolf W. Saalfrank,\* Harald Maid, Nicolai Mooren, and Frank Hampel

Dedicated to Professor Kenneth N. Raymond on the occasion of his 60th birthday

Recent developments in the field of design and synthesis of supramolecular inorganic structures that exhibit novel properties have provided exciting new prospects.<sup>[1]</sup> We have reported on the template-mediated self-assembly of three-membered copper coronate **1** and sandwich complex **2**, starting from dialkyl ketipinates  $\text{H}_2\text{L}^1$  (Scheme 1).<sup>[2]</sup> A common feature of these complexes is that the encapsulated



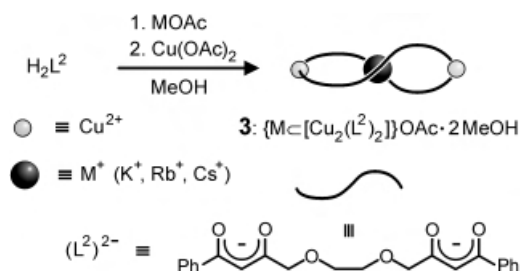
Scheme 1. Synthesis and schematic representation (without coordinating solvent molecules) of metallacoronate **1** and metallasandwich complex **2**.

alkali or alkaline-earth metal ions are coordinated to the inner carbonyl oxygen donors. Compared to the ketipinate dianions  $(\text{L}^1)^{2-}$ , the hybrid dianions  $(\text{L}^2)^{2-}$  or  $(\text{L}^3)^{2-}$  of the glycolate- or catecholate-bridged bis-1,3-diketones, owing to their extra oxygen donors, should be even better ligands<sup>[3–6]</sup> for the design of metallacoronates. To test this hypothesis, we prepared a solution of bis-1,3-diketone  $\text{H}_2\text{L}^2$  and a twentyfold excess of alkali metal acetates ( $\text{M} = \text{K}, \text{Rb}, \text{Cs}$ ) in methanol, and added this mixture dropwise to a solution of copper(II)acetate in methanol. Green crystals were obtained in each case

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(Scheme 2). The microanalytical data and FAB-MS spectra provided indications that the products were the dinuclear copper chelate compounds **3**.<sup>[7, 8]</sup>



Scheme 2. Synthesis and schematic representation of the hybrid metal-lacoronates **3**.

To obtain an unambiguous characterization of the molecular structure of the metallacoronates **3**, we carried out a single-crystal X-ray structure analysis of the potassium complex **3**,  $\text{M} = \text{K}$ <sup>[9–11]</sup> (Figure 1). According to this analysis, in

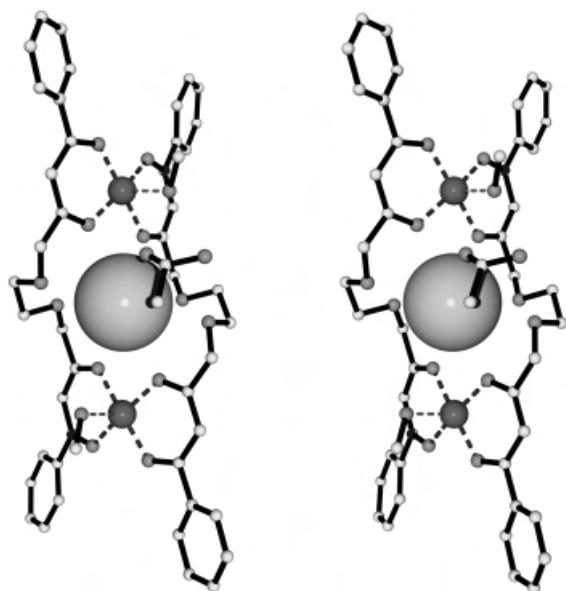


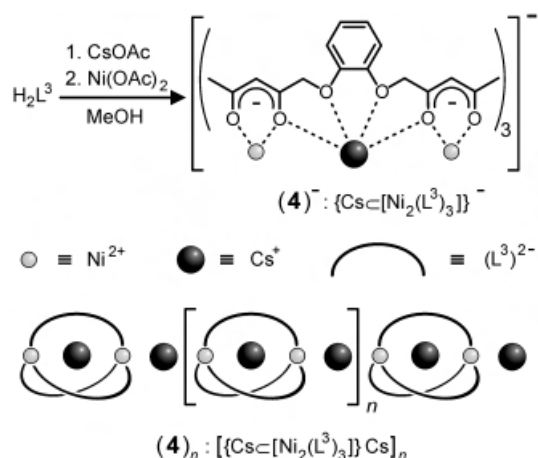
Figure 1. Stereoview of hybrid metallacoronate **3**,  $\text{M} = \text{K}$ , in the crystal. Selected bond lengths [Å] (mean values): Cu–O<sup>o</sup> 1.918, Cu–O<sup>i</sup> 1.924, K–O<sup>i</sup> 2.923, K–O<sup>e</sup> 2.986 (O<sup>o</sup> = outer O, O<sup>i</sup> = inner O, O<sup>e</sup> = ether-O). The dihedral angle of the tetragonal pyramid bases at copper is 84°.

**3**,  $\text{M} = \text{K}$ , the two copper(II) centers are linked through two bis-bidentate glycolate-bridged bis-1,3-diketone dianions ( $\text{L}^2$ )<sup>2–</sup>, affording a [22]metallacrown-8 system (22-MC-8). Formal replacement of the two copper(II) centers in the metallacoronand 22-MC-8 by ethylene bridges gives the topologically equivalent crown ether [24]crown-8. Each copper(II) ion in **K-3** is coordinated in a square-pyramidal fashion to four oxygen atoms of the ligands ( $\text{L}^2$ )<sup>2–</sup> and that of a methanol molecule. The resulting metallacoronand 22-MC-8 is wrapped around a central potassium ion with the effect that four carbonyl oxygen and four ethyleneglycol oxygen donors each are coordinated to this center. Charge compensation is achieved through coordination of an extra disordered acetate

ion to the potassium ion. Thus **3**,  $\text{M} = \text{K}$ , can be characterized as a double-stranded helicate encapsulating a potassium ion. Viewed ideally, the cationic core of the system  $\{ \text{K} \subset [\text{Cu}_2(\text{L}^2)_2] \}^+$  has  $D_2$  symmetry, which is reduced for  $\{ \text{K} \subset [\text{Cu}_2(\text{L}^2)_2] \}^+ \cdot 2 \text{MeOH}$  to  $C_2$  and for  $\{ \text{K} \subset [\text{Cu}_2(\text{L}^2)_2] \} \text{OAc} \cdot 2 \text{MeOH}$  to  $C_1$ . As a rule, chiral molecules from achiral building blocks yield racemic mixtures.<sup>[12]</sup> As expected, the crystals of helical **3**,  $\text{M} = \text{K}$ , contain both enantiomers (*P* and *M*) as documented by the space group  $C2/c$ .

The prognosis of the structure of supramolecular coordination complexes is based on the careful selection of matching metal–ligand combinations. However, previous findings prompted us to tackle nonmatching metal–ligand combinations as well.<sup>[13]</sup> In extension of this strategy, starting with the hybrid dianions ( $\text{L}^2$ )<sup>2–</sup> or ( $\text{L}^3$ )<sup>2–</sup> and hexacoordinate divalent metal ions, instead of tetra-/pentacoordinate copper(II), bicyclic negatively charged {2}-metallacryptates  $\{ \text{M}^i \subset [(\text{M}^{\text{II}})_2(\text{L}^2/\text{L}^3)_3] \}^-$  were expected. The formation of a dimetallic triple-stranded helicate (= {2}metallacryptand) is associated with the generation of a cavity. The host–guest properties of these self-assembled voids strongly depend on the possible interaction between spacer and guest and the charge of the {2}metallacryptand. Notably, most of the macrobicyclic host cavities remain unoccupied and only recently it was shown that alkyl-bridged biscatecholate ligands or *m*-pyridinediyl-spacered bis-1,3-dicarbonyl dianions yield {2}metallacryptates.<sup>[14]</sup>

However, despite these achievements, there were only speculations about the final composition of the neutral species, which may be deduced from anionic  $\{ \text{M}^i \subset [(\text{M}^{\text{II}})_2(\text{L}^2/\text{L}^3)_3] \}^-$ . Therefore, we allowed a solution of catecholate-bridged bis-1,3-diketone  $\text{H}_2\text{L}^3$  in methanol to react with nickel(II) acetate in the presence of a twentyfold excess of cesium ions as template (Scheme 3) and, after work-up, isolated a microcrystalline green solid. Based on the elemental analysis and FAB mass spectrometry, the resulting solid represents a neutral {2}metallacryptate of the composition  $\{ \text{Cs} \subset [\text{Ni}_2(\text{L}^3)_3] \text{Cs} \}$ , which was unequivocally characterized by an X-ray crystallographic structure determination.<sup>[15]</sup> According to this analysis the {2}metallacryptand  $[\text{Ni}_2(\text{L}^3)_3]^{2-}$  core is composed of two nickel(II) centers linked through three bis-bidentate catecholate-spacered bis-1,3-diketone dianions



Scheme 3. Synthesis and schematic representation (without methanol molecules) of the one-dimensional oxo-bridged metal string  $(\text{4} \cdot 3 \text{MeOH})_n$ .

(L<sup>3</sup>)<sup>2-</sup>. Therefore, each nickel(II) ion is coordinated octahedrally by six oxygen donors. The resulting {2}metallacryptands are homochiral with either ( $\Delta,\Delta$ )-*fac* or ( $\Lambda,\Lambda$ )-*fac* configuration at the nickel centers. They hold a cesium ion in the void, which is coordinated by six carbonyl oxygen and six catecholate oxygen donors, each. Charge compensation of the {2}metallacryptates (4)<sup>-</sup> is achieved through extra external cesium ions. Interestingly, the thus accessible neutral ( $\Delta,\Delta$ )/( $\Lambda,\Lambda$ ) building blocks [(Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs] 4 are self-complementary and aggregate alternating across the external cesium ions to give the unprecedented one-dimensional oxo-bridged metal string *meso*-[(Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs · 2MeOH]<sub>n</sub> (4 · 2MeOH)<sub>n</sub>.<sup>[16]</sup> In (4 · 2MeOH)<sub>n</sub> the coupling external cesium ions are coordinated to two sets of three peripheral carbonyl oxygen donors and two methanol molecules. An additional noncoordinated methanol molecule per monomer unit trapped in the crystal leads to the final overall stoichiometry (4 · 3MeOH)<sub>n</sub> for the polymer (Scheme 3, Figure 2). In the crystal, the oxo-bridged metal strings (4 · 2MeOH)<sub>n</sub> run parallel to the (*a,c*)-plane diagonal of the unit cell (Figure 3).

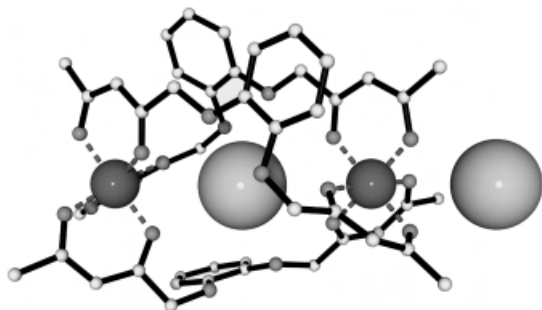


Figure 2. Structure of the self-complementary monomers 4 in the crystal. For reasons of clarity the methanol molecules were omitted. Selected bond lengths [Å] (O<sup>o</sup>/Cs<sup>o</sup> = outer O/Cs, O<sup>i</sup>/Cs<sup>i</sup> = inner O/Cs, O<sup>e</sup> = ether-O, mean values are labeled with \*) of 4: Ni–O<sup>o</sup> 2.044\*, Ni–O<sup>i</sup> 2.030\*, Cs<sup>i</sup>–O<sup>i</sup> 3.201–3.441, Cs<sup>i</sup>–O<sup>e</sup> 3.259–3.648, Cs<sup>o</sup>–O<sup>o</sup> 2.948–3.397.<sup>[18]</sup>

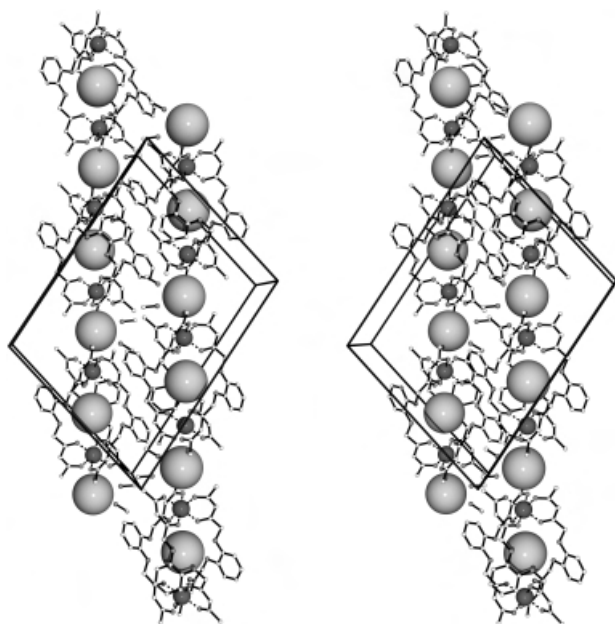


Figure 3. Stereo view of the crystal packing of the oxo-bridged metal strings (4 · 2MeOH)<sub>n</sub>. View along the *b* axis. For reasons of clarity the noncoordinating methanol molecules are omitted.

In conclusion, we have developed a convenient route for the template-mediated self-assembly of hybrid metallacoronates [K ⊂ [Cu<sub>2</sub>(L<sup>2</sup>)<sub>2</sub>]]OAc. Evaluation of the construction plan of these systems initiated the elaboration of self-complementary monomer [(Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs] and finally of the one-dimensional oxo-bridged metal string [(Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs]<sub>n</sub>. There is currently much interest in the fundamental study of oxygen-mediated metal–metal interactions and their potential applications.<sup>[17]</sup>

## Experimental Section

**K-3:** A solution of H<sub>2</sub>L<sup>2</sup> (96 mg, 0.25 mmol)<sup>[3]</sup> and potassium acetate (245 mg, 2.5 mmol) in methanol (64 °C, 5 mL) was added dropwise to a solution of copper(II) acetate monohydrate (50 mg, 0.25 mmol) in methanol (5 mL). The green solution was filtered and layered with diethyl ether (20 mL). Yield: 129 mg (98 %), green crystals; m.p. > 134 °C (decomp); IR (CHBr<sub>3</sub>):  $\tilde{\nu}$  = 1592, 1559, 1516 cm<sup>-1</sup>; FAB-MS (3-nitrobenzyl alcohol matrix): *m/z*: 927 [K ⊂ [Cu<sub>2</sub>(L<sup>2</sup>)<sub>2</sub>]]<sup>+</sup>.<sup>[18]</sup>

**(4)<sub>n</sub>:** A solution of nickel(II) acetate tetrahydrate (166 mg, 0.67 mmol) in methanol (5 mL) was added dropwise to a mixture of H<sub>2</sub>L<sup>3</sup> (306 mg, 1.00 mmol)<sup>[3]</sup> and cesium acetate (1.286 g, 6.70 mmol) in methanol (64 °C, 5 mL). The green solution was filtered and layered with diethyl ether (10 mL). Yield: 116 mg (27 %), emerald green crystals; m.p. > 230 °C (decomp); IR (CHBr<sub>3</sub>):  $\tilde{\nu}$  = 1611, 1469 cm<sup>-1</sup>; FAB-MS (3-nitrobenzyl alcohol matrix): *m/z*: 1561 [Cs{Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs]<sup>+</sup>, 1429 [(Cs ⊂ [Ni<sub>2</sub>(L<sup>3</sup>)<sub>3</sub>])Cs]<sup>+</sup>.<sup>[18]</sup>

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## Natural Products Are Biologically Validated Starting Points in Structural Space for Compound Library Development: Solid-Phase Synthesis of Dysidiolide-Derived Phosphatase Inhibitors\*\*

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The combinatorial synthesis of compound libraries on polymeric supports is at the heart of protein ligand and inhibitor discovery, in particular in the development of new drugs and chemical tools for the study of biological processes. To achieve high efficiency in this process, powerful and alternative strategies for the design of compound libraries are of paramount importance. Herein, a structure-based approach to this fundamental problem is outlined. The key feature is to employ the structural frameworks of biologically active natural products, which are evolutionarily selected for binding to specific protein domains, as a guiding principle for library development. Furthermore, it is demonstrated that the key synthetic challenge posed by this approach, the multistep solid-phase synthesis of natural products and their analogues, can successfully be met.

Proteins can be regarded as modularly built biomolecules assembled from individual domains as building blocks. Since the total number of all available protein domains appears to be fairly limited,<sup>[1]</sup> it has to be expected that in newly discovered proteins with widely varying function and activity the same modules (i.e. domains) or close relatives will be found repeatedly in varying combinations and arrangements as structure- and function-determining entities. Thus, a key to the efficient discovery of new ligands and inhibitors for known and, in particular, for newly discovered proteins is to identify compound classes already biologically validated as being

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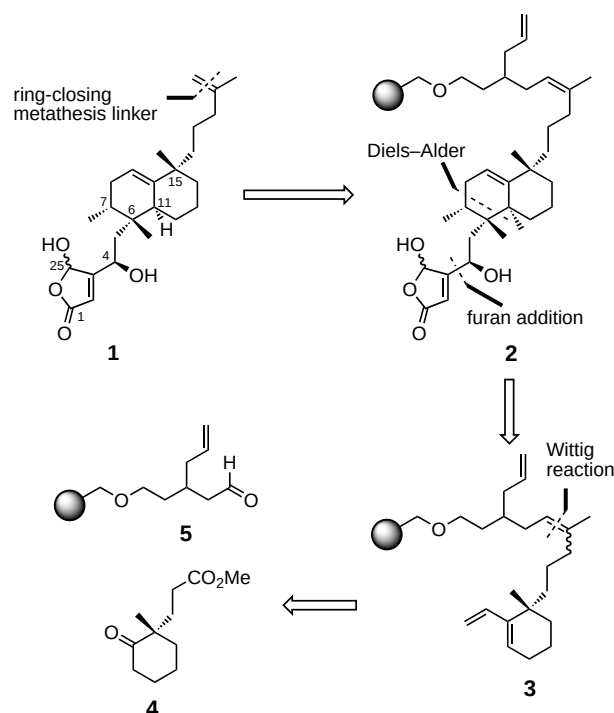
capable of binding to specific protein domains. These compound classes can then be employed as starting points in structural space for library development. Libraries designed and synthesized around the basic structure of such compounds should yield modulators of protein activity with high hit rates. Furthermore they should yield modulators of activity for proteins with differing activity, function and origin which bear the same or very similar domains. Within a group of closely related protein domains usually the individual amino acid sequence and the detailed structure associated with it display substantial variation, which often provides the basis for selective binding and inhibition (e.g. in the ATP-binding sites of protein kinases). Consequently, a central and important aspect of this concept is that it is not necessary to build up a given structure in every detail. Rather, the basic underlying structural framework has to be conserved for the individual library members, and its stereochemistry and functional group pattern have to be varied to achieve selectivity between related proteins.

Biologically active natural products can be regarded as chemical entities that were evolutionarily selected and validated for binding to particular protein domains. Therefore, they are already biologically validated, and the underlying structural architectures of such natural products may provide powerful guiding principles for library development. This structure-based concept differs in its fundamental reasoning from related approaches,<sup>[2]</sup> which focus on the creation of chemical diversity. However, our concept does not neglect this issue, and builds on the diversity created by Nature itself.

Efficient and reliable methods and multistep sequences for the total synthesis of natural products and their analogues on polymeric supports are paramount to the success of this approach. The corresponding transformations must proceed with a degree of selectivity and robustness typical of related classical transformations in solution, irrespective of the stringencies and differing demands imposed by the presence of and the anchoring to the polymeric support. In a few cases, the structural variation of natural products by means of solid-phase methodologies has been achieved,<sup>[3]</sup> mostly in the late steps of the syntheses and through the modification of a core-structure that had been pre-synthesized in solution. But the total synthesis of a natural product and its analogues in long multistep sequences (i.e. ten steps and more) on polymeric supports has only been successful in one case.<sup>[3, 4]</sup> Herein we describe the solid-phase synthesis of analogues of the phosphatase inhibitor dysidiolide, which rapidly yielded compounds with significantly improved biological activity.

The sesquiterpenoid dysidiolide (**1**) is the first naturally occurring inhibitor of the dual-specificity cdc25 protein phosphatase family, which play a crucial role in the regulation of the cell cycle.<sup>[5]</sup> Because of this property and the resulting antitumor activity, dysidiolide has been of intense interest to chemists, biologists, and pharmacologists.<sup>[6]</sup> For the planned solid-phase synthesis, we intended to attach the olefinic side chain to a robust linker that would provide the terminal alkene structure after cleavage from the solid support in a mild and traceless manner. The new olefin metathesis linker incorporated in **2** was thought to fulfill these requirements

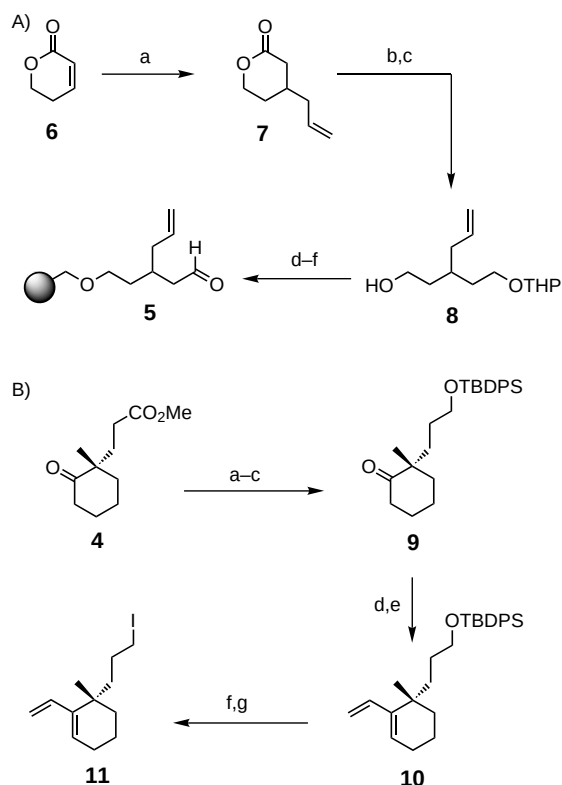
(Scheme 1). The  $\gamma$ -hydroxybutenolide moiety should be obtainable by the addition of 3-lithiofuran to a corresponding aldehyde, and subsequent oxidation of the heterocycle with singlet oxygen. The bicyclic core structure of **1** could be generated by means of a Diels–Alder route previously



Scheme 1. Retrosynthetic analysis of dysidiolide and delineation of a solid-phase synthesis strategy with an olefin-metathesis linker.

investigated in our laboratories<sup>[7]</sup> (**2**  $\Rightarrow$  **3**) and successfully employed in the total syntheses of natural dysidiolide in solution.<sup>[16b–e]</sup> The knowledge gleaned from these studies suggested that this cycloaddition leads primarily to the 6-epimer of the dysidiolide framework. However, we chose to accept this deviation from the goal of synthesizing the parent natural product itself, since in the concept delineated above this is not necessarily required to identify new biologically active compounds. It was planned to synthesize the diene for the Diels–Alder reaction in solution from commercially available chiral ketoester **4**. The diene would then be attached to the linker resin **5** by means of a Wittig reaction in a convergent strategy (**3**  $\Rightarrow$  **4** + **5**).

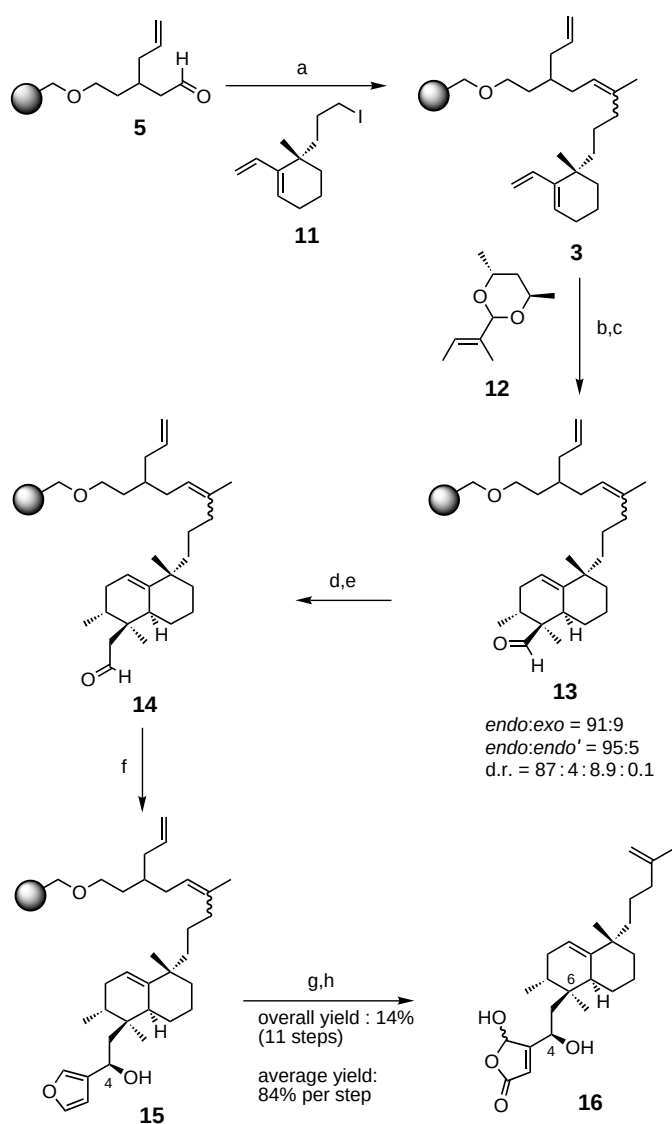
Starting from dihydropyranone **6**, linker **8** was synthesized in the reaction with diallylzinc (generated *in situ*) in the presence of trimethylsilyl chloride (TMSCl), subsequent reduction of lactone **7** with lithium aluminum hydride (LAH), and monoprotection of the resulting diol (Scheme 2A). The protection of one hydroxy group with dihydropyran was necessary to prevent crosslinking in the subsequent attachment of the linker to the Merrifield resin by ether formation. After deprotection and subsequent oxidation of the hydroxy group, the active linker resin **5** was obtained in high yield (90 %, 3 steps in solid phase) with loadings of up to 1.1 mmol g<sup>−1</sup>.



Scheme 2. A) Synthesis of the linker and attachment to the resin. Reagents and conditions: a) allylmagnesium bromide,  $\text{ZnBr}_2$ ,  $\text{TMSCl}$ , THF,  $-78^\circ\text{C}$ , 6 h, 52%; b) LAH, THF, RT, 1 h, 97%; c) 3,4-dihydropyran, Dowex50WX2, toluene, RT, 3 h, 95%; d) NaH,  $n\text{Bu}_4\text{NI}$ , Merrifield-Cl resin ( $1.1 \text{ mmol g}^{-1}$ ), DMF, RT, 18 h; e) pyridinium-*p*-toluene sulfonate, EtOH, dichloroethane,  $\Delta$ , 18 h; f) *o*-iodoxybenzoic acid, THF/DMSO (1:1), RT, 8 h; 90% (three steps). B) Synthesis of the diene: a) LAH, THF,  $0^\circ\text{C}$ , 30 min, 100%; b) TBDPSCI, dimethylaminopyridine,  $\text{Et}_3\text{N}$ , dichloromethane, RT, 17 h, 80%; c) PCC, dichloromethane, RT, 4 h, 94%; d) vinylmagnesium bromide, THF, RT, 5 h; e)  $\text{BF}_3 \cdot \text{OEt}_2$ , benzene/THF (4:1),  $\Delta$ , 43% (d–e); f)  $n\text{Bu}_4\text{NF}$ , THF, RT, 3 h, 95%; g) iodine, imidazole,  $\text{PPh}_3$ , dichloromethane, RT, 1 h, 85%.

The diene was synthesized in solution starting from commercially available chiral ketoester **4**. After reduction with LAH to form the diol, the primary hydroxy group was protected with *tert*-butyldiphenylsilyl chloride (TBDPSCI) and the secondary alcohol was oxidized by using pyridinium chlorochromate (PCC) to obtain ketone **9** in high yield (Scheme 2B). Vinylmagnesium chloride was added to the carbonyl group and the resulting tertiary alcohol was converted into diene **10** by elimination of water under Lewis acid catalysis. After cleavage of the protecting group, the alcohol was finally transformed into alkyl iodide **11**, the precursor for the subsequent Wittig reaction.

In a one-pot two-step procedure, alkyl iodide **11** was treated with the ylide that was obtained by the deprotonation of ethyltriphenylphosphonium iodide to form a secondary phosphonium salt in a nucleophilic attack. This resulting phosphonium salt was then deprotonated with a second equivalent of base, and the aldehyde resin **5** was finally added to yield diene resin **3** (Scheme 3). Subsequently, **3** was treated with the chiral unsaturated acetal **12**<sup>[8]</sup> at  $-78^\circ\text{C}$  in a Lewis acid catalyzed asymmetric Diels–Alder reaction to generate the bicyclic core structure of the target molecule with high



Scheme 3. Solid-phase synthesis of **16**. Reagents and conditions: a)  $\text{EtP-Ph}_3\text{I}$ ,  $n\text{BuLi}$ , **11**, THF, RT, 16 h, then  $n\text{BuLi}$ ,  $0^\circ\text{C}$ , 2 h; b) trimethylsilyltri-fluoromethanesulfonate, dichloromethane,  $-78^\circ\text{C}$ , 7 h; c) *p*-toluenesulfonic acid, acetone, dichloroethane,  $\text{H}_2\text{O}$ ,  $\Delta$ , 20 h; d)  $\text{Ph}_3\text{PCH}_2\text{OMeCl}$ ,  $\text{KOtBu}$ , THF, RT, 4 h; e) pyridinium *p*-toluene sulfonate, THF,  $\text{H}_2\text{O}$  (1%),  $\Delta$ , 16 h; f) 3-bromofuran,  $n\text{BuLi}$ , THF,  $-78^\circ\text{C}$ , 5 h; g)  $\text{O}_2$ ,  $\text{EtPr}_2\text{N}$ , rose bengal,  $h\nu$ , dichloromethane,  $-78^\circ\text{C}$ , 5 h, then RT, 10 min; h)  $(\text{PCy}_3)_2\text{Cl}_2\text{-Ru=CHPh}$  ( $2 \times 10 \text{ Mol } \%$ ), dichloromethane, RT, 16 h.

diastereoselectivity (*endo*/*exo* 91:9; ratio of *endo* isomers 95:5; *endo*/*endo'*/*exo*/*exo'* 87:4:8.9:0.1; the values were determined by means of  $^1\text{H}$  NMR spectroscopic analysis after hydrolysis of the acetals and release of the resulting aldehydes from the solid support by olefin metathesis). Structure and configuration were determined by comparison with literature data.<sup>[6d, 7]</sup>

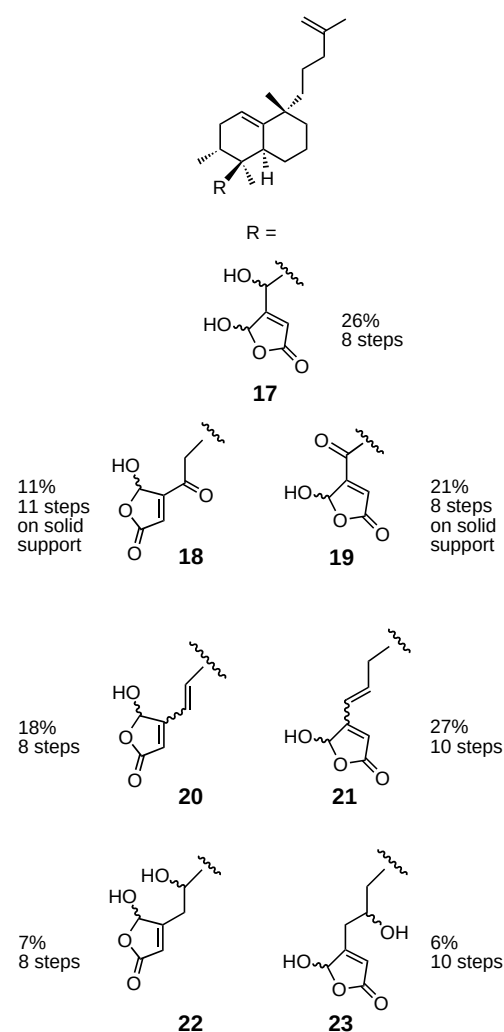
After hydrolysis of the acetal, the carbon chain of aldehyde **13** was elongated by means of a Wittig reaction with methoxymethyltriphenylphosphonium chloride and subsequent hydrolysis of the resulting ether to yield aldehyde **14**. Nucleophilic addition of 3-lithiofuran to the aldehyde resulted in a 2:1 mixture of the epimeric alcohols **15** (determined by means of GC-MS). The furan unit was oxidized with singlet



oxygen in the presence of Hünig's base to form the  $\gamma$ -hydroxybutenolide moiety. Finally, the products were released from the polymeric carrier under very mild conditions in an olefin-metathesis reaction mediated by Grubbs catalyst (Scheme 3).<sup>[9]</sup>

6-*epi*-Dysidiolide and four other diastereomers could be purified by flash chromatography and separated by semi-preparative HPLC on SiO<sub>2</sub> (98 % *n*-hexane/2 % 2-propanol). The analytical data (<sup>1</sup>H NMR, <sup>1</sup>H, <sup>1</sup>H-COSY, IR, HR-MS) of the new analogues were in full agreement with the structure, and similar to the data reported for the natural product. The synthesis sequence from the attachment of **8** to the solid phase to the release of **16** into solution proceeds through a total of eleven chemical steps and makes the desired natural product analogue available with an overall yield of 14 %, that is, with an average yield of 84 % per step. By using this procedure, 48 mg of the desired product can be obtained from one gram of resin with a loading of 1.1 mmol g<sup>-1</sup>.

Based on the developed synthesis strategy, a small library of seven analogues was synthesized from the intermediate aldehydes **13** and **14**. Thus analogue **17** (Scheme 4) with a shorter carbon chain was synthesized by addition of 3-lithiofuran to aldehyde **13** followed by oxidation of the furan ring.



Scheme 4. Dysidiolide analogues obtained in solid-phase syntheses.

The ketones **18** and **19** were obtained by oxidation of secondary alcohols **16** and **17**, respectively, with *o*-iodoxybenzoic acid, after compounds **16** and **17** were released from the polymeric support. The olefinic analogues **20** and **21** were synthesized by Wittig reaction of the aldehydes **13** and **14**, respectively, with the ylide obtained from furylmethyltriphenylphosphonium bromide and subsequent oxidation with singlet oxygen. Derivatives **22** and **23** were obtained by addition of furylmethylmagnesium bromide to the carbonyl group, followed by oxidation of the aromatic ring. Compounds **17**–**23** were obtained in overall yields of 6–27 %.

These results demonstrate that the multistep total synthesis of natural products and analogues on the solid phase is feasible. The transformations applied in the syntheses described above include a variety of very different reaction types that are used widely in organic synthesis: an asymmetric cycloaddition with a removable chiral auxiliary, different organometallic transformations, olefination reactions, different oxidation reactions, acidic hydrolysis of acetals and enol ethers, and a nucleophilic substitution.

To determine if the solid-state synthesis delivered biologically active natural product analogues with a high frequency, we investigated compounds **16**–**23** as inhibitors of the protein phosphatase cdc25C and in cellular cytotoxicity assays. From the cdc25 phosphatase family, the cdc25C protein was chosen because 6-*epi*-dysidiolide **16** has previously been investigated as an inhibitor of cdc25A and cdc25B,<sup>[10]</sup> thereby allowing for comparison of data.

The results obtained in the phosphatase assays (Table 1) demonstrate that all dysidiolide analogues inhibit cdc25C in the low micromolar range with IC<sub>50</sub> values varying by a factor of 20. The IC<sub>50</sub> of 5.1  $\mu$ M determined for inhibition of cdc25C

Table 1. Results of the inhibition of cdc25C and the cytotoxicity tests performed on the colon cancer cell lines SW480 and HCT116, the prostate cell line PC3, and the breast cell line MDA-MB231.

| Compound  | cdc25C <sup>[a]</sup><br>IC <sub>50</sub> [ $\mu$ M] | SW480 <sup>[b]</sup><br>IC <sub>50</sub> [ $\mu$ M] | HCT116 <sup>[c]</sup><br>IC <sub>50</sub> [ $\mu$ M] | PC3 <sup>[c]</sup><br>IC <sub>50</sub> [ $\mu$ M] | MDA-MB231 <sup>[c]</sup><br>IC <sub>50</sub> [ $\mu$ M] |
|-----------|------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------|
| <b>16</b> | 5.1                                                  | 4                                                   | 1.2                                                  | 1                                                 | 1.6                                                     |
| <b>17</b> | 16                                                   | 1                                                   |                                                      |                                                   |                                                         |
| <b>18</b> | 0.8                                                  | > 33                                                | 15                                                   | > 20                                              | > 10                                                    |
| <b>19</b> | 1.5                                                  | 20                                                  | 11                                                   | 13                                                | > 10                                                    |
| <b>20</b> | 6.8                                                  | 4                                                   |                                                      |                                                   |                                                         |
| <b>21</b> | 2.4                                                  | 2                                                   |                                                      |                                                   |                                                         |
| <b>22</b> | 6.1                                                  | > 33                                                |                                                      |                                                   |                                                         |
| <b>23</b> | 9                                                    | > 33                                                |                                                      |                                                   |                                                         |

[a] For the phosphatase assay, the compound (5  $\mu$ L) was dissolved in DMSO (100 %) and added to a solution of recombinant cdc25C (0.2  $\mu$ g) in assay buffer (85  $\mu$ L; 50 mM TRIS-HCl, pH 8.0, 100 mM NaCl, 1 mM DTT, 1 mM EDTA and 10 % DMSO). After incubation for 30 min at 30 °C, the substrate fluorescein diphosphate (FDP) was added to give a final concentration of 1  $\mu$ M. Plates were read after a reaction time of 30 min at 485/535 nm (ex./em.). *o*-Vanadate (IC<sub>50</sub> = 0.1  $\mu$ M) was used as reference compound. [b] The cells were incubated with the compounds at concentrations between 1.2 and 100  $\mu$ M for three days. The viability of the cells was measured with MTT, which is a slightly yellow tetrazolium salt. Living cells reduce the tetrazolium moiety by a mitochondrial dehydrogenase to a dark violet dye which is detected at 570 nm. [c] The assays were performed by using the CytoTox 96 Cytotoxicity Assay Kit from Promega Corporation, USA. 3000 cells were plated per well in a 96-well flat-bottomed plate, incubated with the compounds at concentrations ranging from 0.033  $\mu$ M to 10  $\mu$ M for three days. Cells were lysed, and the cellular lactate dehydrogenase activity was measured which quantitatively reflects the number of cells.

by 6-*epi*-dysidiolide **16** is considerably lower than the values recorded for the inhibition of cdc25A (13  $\mu\text{M}$ ) and cdc25B (18  $\mu\text{M}$ ). Furthermore, the most active compound in this enzyme-assay, ketone **18**, exhibited an  $\text{IC}_{50}$  value in the high nanomolar range (800 nM) and was 6.4 times more active than **16**. These results indicate that dysidiolide analogues and their derivatives can differentiate selectively between different types of phosphatases and conceivably among the three cdc25 family members. The data also indicate that substantial variation of the precise structural details of the natural product itself is tolerated and leads to inhibitors with significantly enhanced potency. Thus, replacement of the hydroxyethyl bridge between the annelated core ring system and the hydroxybutenolide present in compound **16** by an unsaturated three-carbon unit (see **21**) or introduction of a keto group (see **18** and **19**) leads to more potent cdc25C inhibitors.

The synthetic dysidiolide analogues also displayed considerable and differing biological activity in a cytotoxicity assay<sup>[11]</sup> of the colon cancer cell line SW480 (Table 1). Four of the eight compounds investigated showed  $\text{IC}_{50}$  values in the very low micromolar range and pronounced antitumor activity. In this cellular assay, alcohol **17** with a shortened carbon chain was the most active compound, whereas inhibitors **18** and **19** which had shown the lowest  $\text{IC}_{50}$  values and compounds **22** and **23** in which the alcohol is positioned differently between the hydroxybutenolide and the core structure of dysidiolide were considerably less active. This trend also became apparent when ketones **18** and **19** as well as *epi*-dysidiolide **16** were subjected to cytotoxicity assays of the colon cell line HCT116, the prostate cancer cell line PC3, and the breast cancer cell line MDA-MB231. Ketones **18** and **19** again were substantially less active than *epi*-dysidiolide **16**, which inhibits cell proliferation in all three cases with  $\text{IC}_{50}$  values in the very low micromolar range (Table 1).

Thus, the data indicate that the small library of natural product analogues already contains potent compounds with significantly different biological activities both in vitro and in vivo. The observation that the order of  $\text{IC}_{50}$  values determined in an enzyme assay does not necessarily parallel the outcome of cellular assays is not uncommon.

In conclusion, we have demonstrated that the synthesis of natural product derived libraries in long multistep sequences executed on a polymeric support and employing a variety of widely differing synthetic transformations is feasible and that it can deliver potent biologically active compounds with high frequency.

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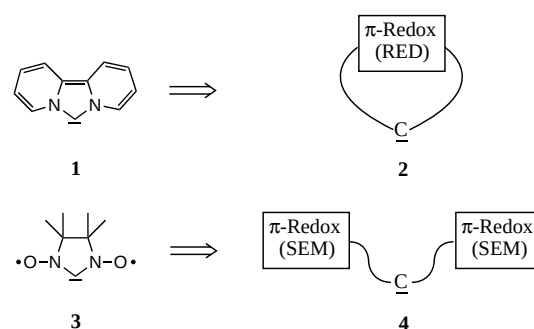
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## Dinitroxide Carbenes, A New Class of Carbenes with Autoimpolung Character: Preparation in Solution and Stabilization in Transition Metal Complexes\*\*

Robert Weiss\* and Norbert Kraut

With the synthesis of **1** we recently reported the prototype of a carbene with autoimpolung character.<sup>[1]</sup> As the general structure **2** shows, in such a system a singlet carbene center is conjugated with the termini of a two-step  $\pi$ -redox system in the reduced state (RED).<sup>[2]</sup> The electrons in this reservoir can be used in the sense of a redox umpolung to respond to electronic requirements of the coordination partner at the carbene center.<sup>[3]</sup> To extend this concept we report here the first synthesis of the dinitroxide carbene **3** in solution and its stabilization in transition metal complexes.



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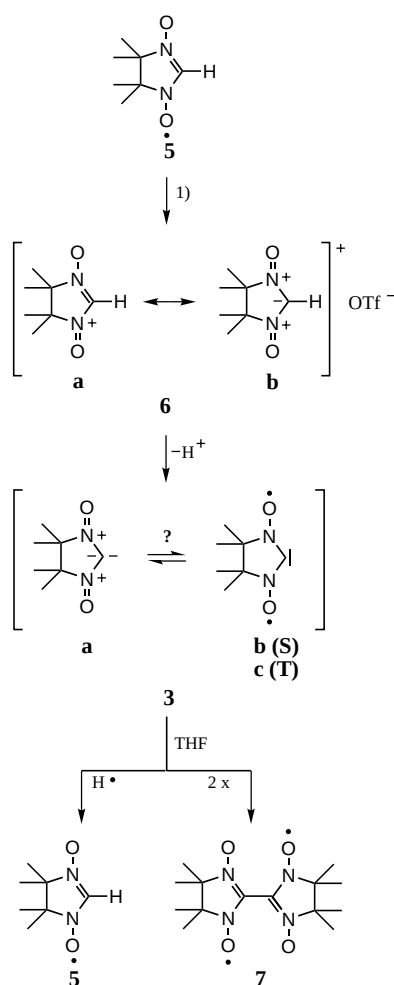
[\*\*] We thank Prof. P. Audebert, ENS Cachan (Paris), for undertaking the cyclic voltammetric measurements and Dr. F. Hampel, Universität Erlangen-Nürnberg, for performing the crystal-structure analysis.

Compound **3** is the first example of a general class of compounds **4**, in which the two substituents at the carbene center can be looked upon as being the termini of two, mutually independent two-step  $\pi$ -redox systems. This electronic configuration should be able to interact with even higher flexibility than **2** with a coordination partner at the carbene center. In **3** the two redox systems exist formally in a semi-oxidized form (SEM form)<sup>[4]</sup> so that aside from the autoupolung ability the multiplicity of this compound is also of importance. We have recently reported the synthesis and C2 functionalization of the radical anion of **3**.<sup>[5]</sup>

In the synthesis of **3** a suitable nitronylnitroxide is initially oxidized to the corresponding nitronylnitrosonium ion and then deprotonated at the central C2 unit. Whereas nitronylnitroxides, as a consequence of their magnetic properties, are of particular current interest as central building blocks in supramolecular materials,<sup>[6]</sup> little is known about the corresponding nitronylnitrosonium ions.<sup>[7a]</sup> Only one compound of this type has been unambiguously characterized by X-ray structure analysis.<sup>[7b]</sup> We have established that nitronylnitroxides may be readily transformed into the corresponding nitronylnitrosonium triflates with  $\text{Br}_2/\text{Me}_3\text{SiOTf}$  ( $\text{OTf}^-$  = trifluoromethanesulfonate) in the ratio of 1:2.<sup>[8]</sup> With this method we obtained in good yield the highly oxidizing ( $E_{1/2} = 0.80$  V vs. saturated calomel electrode (SCE)) orange nitronylnitrosonium salt **6** from the stable, red-violet radical **5**.<sup>[9]</sup> According to semi-empirical calculations nitronylnitrosonium ions are best regarded as geminal dinitrosonium-stabilized carbanions ("dinitrosonium methides"). According to this description the resonance structure **b** from Scheme 1 dominates for **6** (charge on C2 (PM3):  $-0.86$ ). From the calculations the C2 H atom is correspondingly highly positive (charge (PM3):  $+0.26$ ); the reasons for this lie presumably in the strong  $-I$  effect of the neighboring nitrosonium functions and in ring-strain effects.<sup>[3]</sup> In agreement with this interpretation the resonance signal for this proton is at  $\delta = 9.52$  in the  $^1\text{H}$  NMR spectrum.

As expected, **6** may be readily deprotonated: if  $\text{KO}t\text{Bu}$  is added to a solution of **6** in THF the red-violet biradical **7**, previously synthesized by Ullman et al. by an alternative route<sup>[10]</sup> is obtained in high yield (86%). Remarkably, with inverse addition (i. e. the addition of **6** to a solution of  $\text{KO}t\text{Bu}$ ) 37% of **5** is obtained in addition to 34% of **7**. The experimental results can be interpreted as follows:

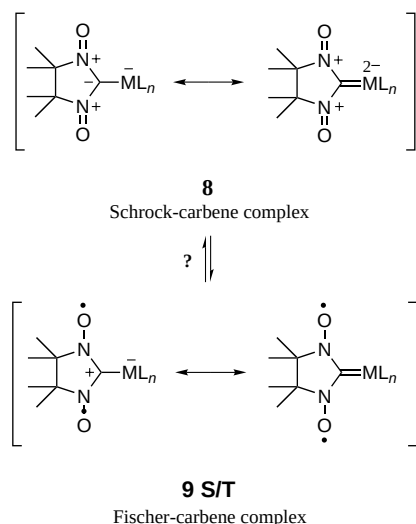
- 1) By deprotonation of **6** the dinitrosoniumdiide **3a** is first formed from which the dinitroxide carbene is generated by autoupolung, either in the form of the singlet biradicaloid **3b** and/or the corresponding  $\pi$ -triplet carbene **3c**.<sup>[11]</sup> The determination of the relative energies of the electronic configuration of **3**—only possible for the gas phase—is a difficult theoretical problem which is currently occupying us.<sup>[12]</sup>
- 2) The subsequent reactions, that is, the dimerization of **3** to **7** and the formation of **5** from **3** by H abstraction from a solvent molecule,<sup>[13]</sup> strongly suggests the presence of an open-shell system in which the central C atom exhibits partial radical character. Because of spin delocalization in the  $\pi$ -system this takes place only with **3b/3c**, not, however, with **3a**.



Scheme 1. Preparation and deprotonation of **6**; 1)  $\text{Br}_2:\text{TMSOTf}$  1:2. S = singlet, T = triplet.

- 3) The dependency of the observed product distribution on the mode of addition of the reactants in the deprotonation of **6** suggests that **7** is not only accessible by direct dimerization of **3b/3c**, but—energetically more favorably—also by recombination of the carbenes **3a–c** with the precursor **6** and subsequent deprotonation. This “proton-catalyzed” dimerization has also been observed with Arduengo carbenes.<sup>[14]</sup> With inverse addition (i. e. with base already present) **3** finds only a small amount of the precursor cation as reaction partner present so that H abstraction from the solvent can compete with the (uncatalyzed) dimerization.

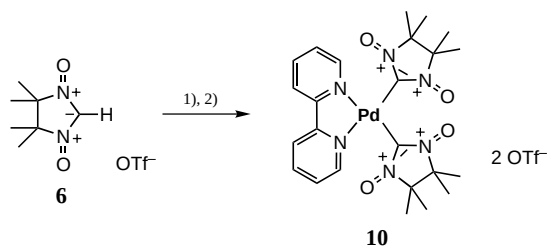
Since the dinitroxide carbenes **3a–c** have a single  $n$  electron pair on the central C atom they should also be able to act as  $\sigma$ -electron donor systems towards  $\text{ML}_n$  units (where M = metal center,  $L_n$  = ligand set). Dependent upon the electronic nature of the respective  $\text{ML}_n$  fragment basically two electronically complementary classes of carbene complexes can be imagined using the autoupolung concept (see Scheme 2). In **8** the carbene ligand acts as  $\pi$ -electron donor towards the  $\text{ML}_n$  unit (Schrock-type carbene complex), in **9**, however, as a  $\pi$ -electron acceptor (Fischer-type carbene complex). In the latter case, in addition to a singlet biradicaloid structure **9S**, a novel triplet carbene complex **9T** is also conceivable. The



Scheme 2. Possibilities for autoumpolung in the transition metal complexes of **3**.

electronic properties of  $ML_n$  (oxidation state of M, type, number, and spatial arrangement of L) may well decide which of these electronic configurations is realized. Equilibria between the autoumpolung isomers **8** and **9 S/T** can also be envisaged. Semi-empirical calculations (PM3) with different  $ML_n$  units confirm this assumption at least qualitatively.

The synthesis of transition metal complexes of **3** by direct reaction of transition metal compounds with the dinitroxide carbene formed in situ failed due to the transient nature of the carbene. However, the synthesis succeeded by  $S_E$  reactions at the electron-rich C2 center of **6**. In this way we obtained the first dinitroxide carbene complex **10** in good yield (85%) by the reaction of **6** with palladium(II) acetate/2,2'-bipyridine in acetonitrile under mild conditions (Scheme 3, see also the Experimental Section and ref. [15]).



Scheme 3. Preparation of **10**: 1)  $Pd(OAc)_2$ ,  $CH_3CN$ , reflux, 12 h; 2) 2,2'-bipyridine, THF, RT, 1 h.

Figure 1 shows the crystal structure of the cation of **10**.<sup>[16]</sup> Owing to their electronic character the carbene ligands, arranged almost vertically to the coordination plane of the palladium, should be regarded as nitronitroso systems. This assignment comes from spectroscopic measurements as well as the structural parameters of the five-membered ring in **10**, which resemble closely those of a previously described C2-phenylated nitronitroso compound. In particular, the N–O bond lengths in **10** at about 124 pm resemble those of this reference compound (ca. 122.5 pm).<sup>[7b]</sup> Moreover, **10** is

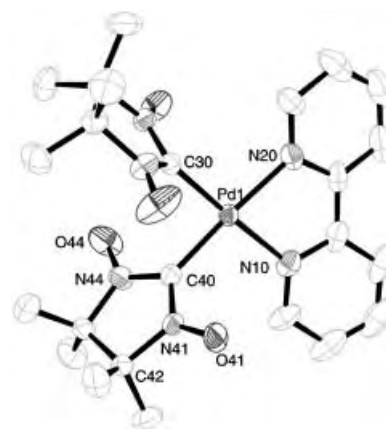


Figure 1. Molecular structure of the cation of **10**. Selected bond lengths [Å] and angles [°]: Pd1–N20 2.066(4), Pd1–C40 1.977(4), C40–N41 1.341(6), C40–N44 1.351(6), N44–O44 1.231(5), N41–O41 1.243(4); N20–Pd1–N10 79.8(16), C40–Pd1–C30 85.44(17), N44–C40–N41 104.6(4), C40–N41–C42 117.0(3), C40–N41–O41 122.8(3).

diamagnetic. Clearly in this complex the reversed-polarity singlet structure **3a** of a dinitroxide carbene is stabilized in accordance with the general structural type **8** (see also Scheme 2). The variable electronic nature of the dinitroxide carbenes predisposes this ligand type as a novel, electronically flexible coordination partner both for metallic and non-metallic centers.

In a similar manner, however without 2,2'-bipyridine, 2:1 carbene complexes of  $Hg^{II}$ ,  $Ag^I$ , and  $Au^I$  could be obtained and characterized in good yield as stable, orange salts. These salts, similar to **10**, are highly oxidizing and, with respect to their electronic configuration, also appear to correspond to **10**. On-going investigations are concerned with the controlled reduction of these diamagnetic systems to the respective homoleptic nitronitroso complexes, a previously unknown class of compounds.

#### Experimental Section

**6**: A solution of  $Br_2$  (0.06 mL, 1.22 mmol) and  $Me_3SiOTf$  (0.48 mL, 2.68 mmol) in dichloromethane (5 mL) was added dropwise to a solution of **5** (383 mg, 2.44 mmol) in dichloromethane (10 mL) at  $-40^\circ C$ . After concentration of the solution diethyl ether (60 mL) was added. The orange precipitate was collected by filtration, washed with a little diethyl ether, and dried under high vacuum. Yield: 516 mg (69.1%); correct  $C_{12}H_{11}N_2O_2$  analysis;  $^1H$  NMR (400 MHz,  $CD_3NO_2$ ,  $32^\circ C$ ):  $\delta$  = 1.88 (s, 12H;  $CH_3$ ), 9.52 (s, 1H; CH);  $^{13}C$  NMR (100 MHz,  $CD_3NO_2$ ,  $32^\circ C$ ):  $\delta$  = 24.6 (s;  $CH_3$ ), 93.2 (s; C), 122.2 (q,  $^1J(C,F)$  =  $-318.9$  Hz;  $CF_3$ ), 153.5 (s; CH); IR (KBr):  $\tilde{\nu}$  = 3166m, 3060w, 1756w, 1627w, 1490s, 1410w, 1391m, 1381m, 1272s, 1229s, 1160s, 1034s, 813w, 757w, 640s, 575m, 540m, 519m  $cm^{-1}$ ; EI-MS (70eV):  $m/z$  (%): 157 (40) [ $M^+ - OTf$ ], 83 (55) [ $C_6H_{11}^+$ ], 69 (100) [ $CF_3^+$ ]; FAB-MS (NBA):  $m/z$  (%): 463 (100) [ $2M^+ - OTf$ ].

**10**: A solution of **6** (331 mg, 1.08 mmol) and  $Pd(OAc)_2$  (121 mg, 0.54 mmol) in acetonitrile (20 mL) was heated under reflux for 12 h. The solution was then evaporated to a few mL and treated with diethyl ether. The orange solid was collected by filtration and washed with diethyl ether. The solid was then suspended in THF (10 mL), treated with 2,2'-bipyridine (84 mg, 0.54 mmol), and stirred at room temperature for 1 h. After the addition of diethyl ether (30 mL) the pale pink precipitate was collected by filtration, washed with a little diethyl ether, and dried under high vacuum. Yield: 401 mg (85.0%); correct  $C_{12}H_{11}N_2O_2$  analysis;  $^1H$  NMR (400 MHz,  $CD_3NO_2$ ,  $-20^\circ C$ ):  $\delta$  = 1.74 (s, 12H;  $CH_3$ ), 1.86 (s, 12H;  $CH_3$ ), 7.68 (m, 4H; CH), 8.45 (m, 4H; CH);  $^{13}C$  NMR (100 MHz,  $CD_3NO_2$ ,  $20^\circ C$ ):  $\delta$  = 25.2 (brs;  $CH_3$ ), 92.2 (brs; C), 122.4 (q,  $^1J(C,F)$  =  $-319.8$  Hz;  $CF_3$ ), 125.7 (s; CH), 129.6 (s;

CH), 144.0 (s; CH), 152.8 (s; CH), 157.5 (s; CH), 212.2 (s; CPd); IR (KBr):  $\tilde{\nu}$  = 1637mb, 1450m, 1422s, 1384m, 1263s, 1225w, 1158m, 1033s, 860w, 772m, 637s, 549m, 519m  $\text{cm}^{-1}$ ; FAB-MS (NBA):  $m/z$  (%): 727 (10) [ $M^+ - \text{OTf} + 4\text{H}$ ], 574 (90) [ $M^+ - 2\text{OTf} + \text{H}$ ], 262 (100) [bipyPd<sup>+</sup>].

Deprotonation of **6**: 1) A solution of **6** (193 mg, 0.63 mmol) in THF (5 mL) was added dropwise to a solution of KO<sup>t</sup>Bu (71 mg, 0.63 mmol) in THF (10 mL) at  $-78^\circ\text{C}$ . The solution was then evaporated to dryness and the residue was separated by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$ :ethyl acetate 4:1). Yields: 34 mg **7** (34%), 37 mg **5** (37%). 2) KO<sup>t</sup>Bu (58 mg, 0.52 mmol) was added slowly to a solution of **6** (160 mg, 0.52 mmol) in THF (10 mL) at  $-78^\circ\text{C}$ . The solution was then evaporated to dryness and the residue separated by chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$ :ethyl acetate 4:1). Yield: **7** (70 mg, 86.2%). Compounds **5** and **7** have been described in the literature and could be unambiguously identified by spectroscopic data (EI-MS, ESR, and UV measurements).<sup>[9, 10]</sup>

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- [12] R. Weiss, N. Kraut, T. Clark, N. J. R. Eikema Hommes, R. Puchta, unpublished results.
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- [16] Crystal structure data for **10**:  $\text{C}_{26}\text{H}_{32}\text{F}_6\text{N}_6\text{O}_{10}\text{PdS}_2$ ,  $M_r = 873.10$ , monoclinic, space group  $C2/c$ ,  $a = 40.219(8)$ ,  $b = 7.5618(15)$ ,  $c = 23.737(5)$  Å,  $\beta = 108.16(3)^\circ$ ,  $V = 6859(2)$  Å<sup>3</sup>,  $Z = 8$ ,  $\rho_{\text{calc}} = 1.691$  Mg m<sup>-3</sup>, crystal dimensions:  $0.20 \times 0.20 \times 0.10$  mm,  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71073$  Å),  $T = 173(2)$  K,  $F(000) = 3536$ ; the data were collected with a Nonius Kappa CCD Area Detector in the range of  $2.13^\circ < \theta < 25.02^\circ$  (11 453 reflections were measured, of which 6004 were independent and 4783 with  $I > 2\sigma(I)$ ). The absorption correction was carried out with the program Scalepack (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307). The structure was solved by direct methods (SHELXS97); structure refinement against  $F^2$  (SHELXL97). The hydrogen atoms were fixed at idealized positions (riding-model). Refinement  $R$  values:  $R1 = 0.0477$  for  $I > 2\sigma(I)$ ,  $wR2 = 0.1420$  for all data. Residual electron density  $1.665/-0.890$  e Å<sup>-3</sup>. 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-164924. 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).

## Visualization of Molecular Recognition Events on Microstructured Lipid-Membrane Compartments by In Situ Scanning Force Microscopy\*\*

Stephanie Künneke and Andreas Janshoff\*

Cell membranes are the most important interfaces in biological systems. A variety of reactions, such as molecular biorecognition of soluble proteins by receptor lipids, take place at this unique surface. Artificial solid-supported lipid bilayers are well suited model systems that allow the study of certain reactions under defined quasi-native conditions. Additionally, they enable the assembly of biosensor surfaces with ordered receptor molecules in a densely packed matrix efficiently suppressing nonspecific adsorption of biomolecules.<sup>[1]</sup>

Arrays of microstructured individually addressable lipid-membrane compartments meet the requirements given by analytical applications, combinatorial libraries, or pharmacological screening, which create a demand for high-throughput analysis and highly comparable and reliable results.<sup>[2]</sup> A structured surface that enables a direct comparability of biomaterials and a parallel analysis of protein–receptor interactions on different membranes or receptors under identical ambient conditions is well suited if not required especially for scanning force microscopy of material contrasts and visualization of lipid–protein interactions. Because lipid membranes rarely show topographical features, a microstructured lipid bilayer with defined boundaries becomes necessary to compare contrasts qualitatively and to enable parallel control measurements. While the structuring of proteins and nucleic acids is relatively straightforward, the preparation and structuring of lipid bilayers requires handling in aqueous solution.

Methods based on contact printing for structuring lipid membranes are limited to a very small number of different lipid compositions, moreover the individual addressability of the segments is cumbersome.<sup>[3]</sup>

We have developed a general microstructuring procedure for generating numerous selectively functionalized lipid-

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membrane compartments on a solid support in close vicinity to each other. The number of different lipid segments is presently only limited to the handling of the manual injection of vesicle solutions.<sup>[4]</sup>

The manufacturing of an array of solid-supported lipid bilayers in the micrometer regime is accomplished by a combination of vesicle spreading<sup>[5]</sup> and the formation of a microfluidic network ( $\mu$ FN).<sup>[6]</sup>

The technique of material molding in capillaries formed by elastomers was first established by Whitesides et al.<sup>[6]</sup> The basic idea of this technique, which belongs to the family of soft lithography, is to create a structured elastomer that functions as the mold, which provides a hydrodynamically coupled network of empty channels once brought into contact with the substrate. The structure of the mold is obtained by curing the two components of the polydimethylsiloxane (PDMS) on a coated silicon wafer, which displays the inverse master structure, and subsequent removal of the PDMS-replicate from the silicon wafer. Prior to use it is necessary to expose the PDMS mold to an  $O_2$  plasma to render the surface hydrophilic and hence provide a temporal seal between the mold and the glass substrate.<sup>[7]</sup> As a consequence, the capillaries are filled rapidly with vesicle suspensions due to the high surface tension of the capillary walls. Delamarche et al. used this method successfully for microstructuring of proteins.<sup>[8]</sup>

Figure 1 illustrates schematically the microstructuring process of solid-supported membrane segments.<sup>[4, 9]</sup> The flow pads are filled individually with different vesicle solutions through small preformed holes from the top of the PDMS

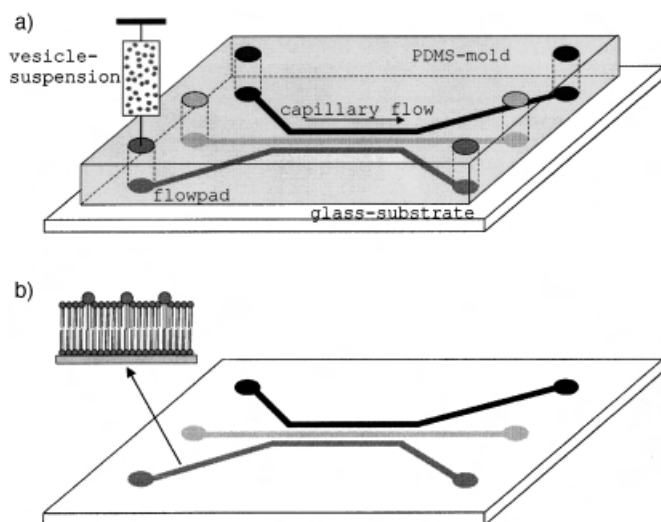


Figure 1. Schematic representation of the microstructuring of solid-supported membrane segments of different compositions.

mold. The empty channels are filled rapidly with the injected vesicle-suspension in a laminar fashion. The liposomes adhere on the glass surface and subsequently spread onto the interfaces forming planar lipid bilayers (Figure 1a). After removal of the PDMS mold and immediate rinsing of the sample with excess buffer, the separated lipid-membrane compartments remaining on the substrate (Figure 1b) are

readily accessible to optical techniques and high-resolution surface analysis tools.

To demonstrate the suitability of this method we first focus on optical investigations of the specific protein-receptor interaction of the tumor-marking protein peanut agglutinin (PNA) from *Arachis hypogaea* on lipid-membrane segments of 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) without any receptor molecules and DMPC with the receptor ganglioside asialo- $G_{M1}$ <sup>[10]</sup> incorporated in a membrane segment using confocal laser scanning microscopy. Additionally, the specific binding of cholera toxin B-oligomer<sup>[11]</sup> (CTB) to the receptor ganglioside  $G_{M1}$  embedded in a DMPC-membrane segment was investigated by scanning force microscopy.

Specific recognition of saccharide structures on cell surfaces, which is shown here using these two prominent examples, is a relevant issue for the differentiation of normal and malign cell types, for the binding of toxic proteins such as cholera, pertussis, botulinum, tetanus, and diphtheria toxin as well as for inflammatory processes.

Figure 2 shows the fluorescence microscopic images of two lipid-membrane segments consisting of DMPC doped with 4 mol % of the receptor asialo- $G_{M1}$  and 1 mol % of

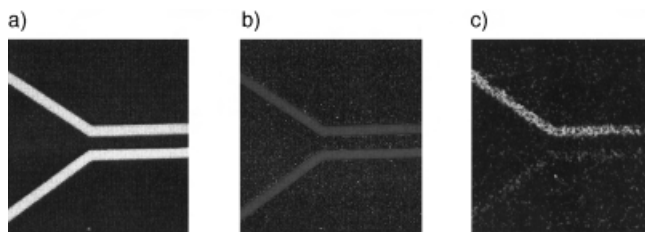


Figure 2. Fluorescence microscopy images of two DMPC/ $\beta$ -Bodipy-500/510- $C_{12}$  HPC segments (upper segment contains the receptor asialo- $G_{M1}$ ) before (a,b) and after (c) addition of 278 nm TRITC-x-PNA. a) Fluorescein-fluorescence; b, c) rhodamine-fluorescence.

the fluorophore  $\beta$ -Bodipy-500/510- $C_{12}$ HPC (upper segment;  $\beta$ -Bodipy-500/510- $C_{12}$ HPC = 2-(4,4-difluoro-5-methyl-4-bora-3a,4a-diaza-*s*-indacene-3-dodecanoyl)-1-hexadecanoyl-*sn*-glycero-3-phosphocholine) and DMPC with 1 mol %  $\beta$ -Bodipy-500/510- $C_{12}$  HPC (lower segment) in the fluorescein fluorescence (Figure 2a) before adding the protein. Figure 2b shows the control experiment with rhodamine fluorescence. The specific binding of the lectin tetramethylrhodamine-B isothiocyanate (TRITC)-x-peanut agglutinin (TRITC-x-PNA) to the membrane segment containing asialo- $G_{M1}$  (upper segment in Figure 2c) is accompanied by an increase of the rhodamine fluorescence intensity after incubating a 278 nm protein solution for 10 min.

Compared to fluorescence microscopy and other optical methods, scanning force microscopy is advantageous for the analysis of protein-lipid interactions because the protein binding can be directly imaged by the height change without labeling techniques, and additionally, imaging of single proteins is possible.

Figure 3a–c display SFM topography images of DMPC/ $G_{M1}$  and DMPC lipid segments on a glass substrate before (Figure 3a) and after (Figure 3b, c) addition of 2.7 nM CTB. Histogram analysis (Figure 3d) was performed by using

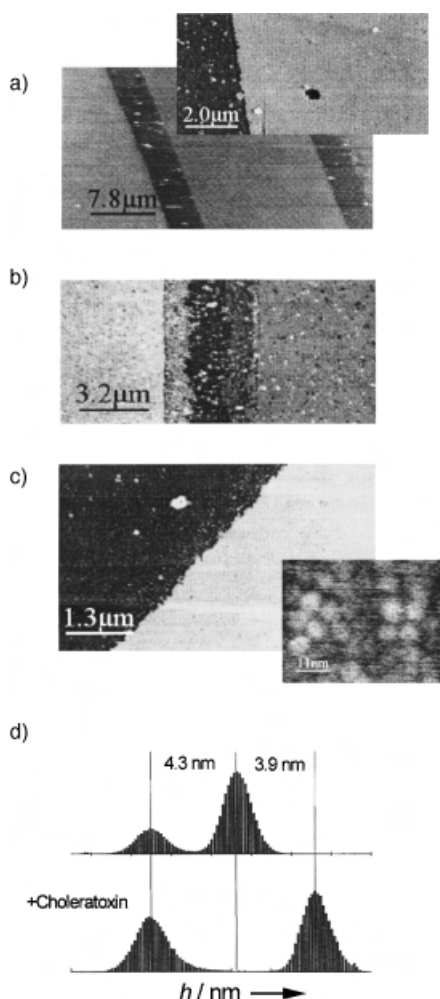


Figure 3. Scanning force microscopy images (tapping-mode, total height 14 nm) showing the topography of different lipid membrane segments on a glass substrate (a) before and (b,c) after addition of 2.7 nM CTB. The lipid segment on the left-hand side of b) consisting of DMPC/GM<sub>1</sub> is covered with cholera toxin homogeneously, while the segment on the right side lacks receptor lipids and shows no sign of protein adsorption after addition of CTB. The average increase in height was 3.9 nm (d) after the addition of CTB. The inset in c) (deflection signal, contact-mode) shows individual B-oligomers providing the ultimate proof that CTB is adsorbed on the surface (lipid segment).

Figure 3a (portrait figure) and Figure 3c. The average height of substrate and membrane was determined by fitting Gauss functions to the data. The average height difference between the substrate and the DMPC/GM<sub>1</sub> membrane is 4.3 nm before addition of the protein and 8.2 nm after the incubation of CTB (Figure 3d). The specific binding of the proteins was revealed by the integral measurement of the height, and confirmed by resolving single molecules, namely CTB (inset in Figure 3c).<sup>[12]</sup> The applicability of the presented lipid array for investigation of specific binding of biomaterials is demonstrated by the absence of both height change and protein structure of the DMPC membrane segment without receptor, which is not possible by fluorescence measurement alone (right segment in Figure 3b).

The combination of this preparatively simple method with scanning force microscopy is particularly interesting, since here not only molecular recognition for biosensor applica-

tions is used, but also the theoretical basis of material properties, such as adhesion contrast, viscoelasticity of different lipids, and receptor organization in membranes, could be investigated on a single structured surface.

### Experimental Section

Small unilamellar vesicles of 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC: Avanti Polar Lipids, Alabaster, AL, USA) doped with 2 mol % GM<sub>1</sub> or 4 mol % asialo-GM<sub>1</sub> (Sigma, Dreieich, Germany), and 1 mol %  $\beta$ -Bodipy-500/510-C<sub>12</sub>HPC (Molecular Probes, Eugene, OR, USA) were prepared by the extrusion method using two stacked polycarbonate membranes (average pore diameter 50 nm) and subsequent sonification.

The B-oligomer of the cholera toxin (*Vibrio cholerae*) was purchased from CalBioChem (La Jolla, CA, USA), the fluorophore-labeled protein tetramethylrhodamine-isothiocyanate (TRITC)-x-peanut agglutinin (*Arachis hypogaea*) was obtained from Sigma (Dreieich, Germany).

A commercial atomic force microscope AFM (Bioscope with Nanoscope IIIa controller, Veeco Digital Instruments) with lipid cell and silicon nitride cantilevers that exhibit a nominal spring constant of 0.12 N m<sup>-1</sup> (tapping-mode) and 0.06 N m<sup>-1</sup> (contact-mode) was used for the atomic force microscopy (AFM) experiments. The scan rates were set to 0.5 Hz in tapping-mode and 4 Hz in contact mode for recording the deflection signal.

Confocal laser scanning microscopy was performed by using a MRC 600 (Bio-Rad, München, Germany).

All experiments were performed in a pH 7.4 buffer from 10 mM (tris(hydroxymethyl)aminomethane(Tris)/HCl and 100 mM NaCl.

A 10:1 mixture of the elastomer and curing agent of polydimethylsiloxane PDMS (Sylgard 184, Dow Corning Silicon Elastomer, West Midlands) was cured on a structured silicon wafer (IMSAS, Bremen, Germany) which had been coated with a thin film of 1H,1H,2H,2H-perfluorodecyldimethylchlorosilane prior to use.

The capillary structures used in these experiments are 15  $\mu$ m wide, 3  $\mu$ m high, and 2 mm long. The five parallel capillaries are separated from each other by a distance of 5  $\mu$ m ending on either side in flow pads of 2.13  $\times$  2.13 mm. The PDMS-replicates are used up to 50 times. There are 0.1  $\mu$ L of vesicle solution injected in each flow pad.

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# The (2-Phenyl-2-trimethylsilyl)ethyl-(PTMSEL) Linker—A Novel Linker for the Solid-Phase Synthesis of Protected Peptides and Glycopeptides Cleavable with Fluoride\*\*

Michael Wagner and Horst Kunz\*

Dedicated to Professor Lutz F. Tietze  
on occasion of his 60th birthday

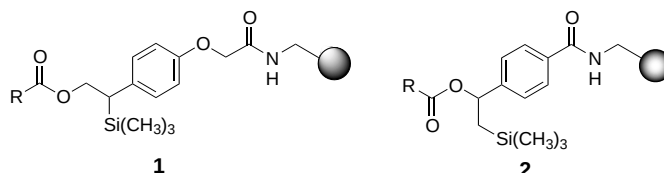
Synthesis on solid phase is of great importance for the rapid access to peptides and peptide conjugates.<sup>[1]</sup> In particular this holds true for the combinatorial synthesis of compound libraries and large groups of single compounds. In the meantime, the principle of combinatorial synthesis has been expanded to the generation of many different classes of organic compounds.<sup>[2]</sup>

In all variations of combinatorial solid-phase syntheses, the linker is of crucial importance. It must be stable throughout the multistep synthesis, but finally should be cleavable under mild conditions without affecting the products. Most commonly used in solid-phase peptide synthesis are acid-labile linkers,<sup>[1, 2]</sup> such as the *p*-alkyloxybenzyl ester and triphenylmethyl(trityl, Trt) ester type linkers.<sup>[3]</sup> During their cleavage, acid-labile protecting groups, for example in the amino acid side chains of the synthesized peptides, can be removed simultaneously. Under acidic and basic cleavage conditions, undesired side reactions often take place in the produced peptides, among which, aspartimide formation and rearrangements in aspartyl peptides are very difficult to prevent.<sup>[4, 6]</sup> Most of these side reactions can be avoided by using linker systems, which are cleavable under neutral conditions such as the allylic anchors.<sup>[5]</sup> Because of their insufficient steric hindrance, the allyl-ester type linkers are sometimes susceptible to aminolysis. Accordingly, they are prone to diketopiperazine formation at the stage of the polymer-bound dipeptides after removal of the 9-fluorenylmethoxycarbonyl(Fmoc) group as amino protecting group.

*p*-Silylmethylbenzyl,<sup>[7]</sup> *p*-silyloxybenzyl<sup>[8]</sup> and  $\alpha$ -trimethylsilylbenzyl (SAC)<sup>[9]</sup> linkers based on the (2-trimethylsilyl)ethyl (TMSE) ester<sup>[6a]</sup> and cleavable with fluoride ions represent a further option for the mild detachment of peptides from the polymer support. However, even the most sensitive among them, the SAC linker,<sup>[9]</sup> needs tetrabutylammonium fluoride (TBAF) trihydrate in dimethylformamide (DMF) for its cleavage, which for a tetrapeptide results in accompanying aspartimide formation of up to 80%. In contrast, when benzyltrimethylammonium hydrogen difluoride in DMF was used as the cleaving reagent, the cleavage yield in the synthesis of two simple tetrapeptides was unsatisfactory (30%–40%), and the crude products still contained up to

10% of the aspartimide. Therefore, these authors recommend the acidolysis with 1% trifluoroacetic acid (TFA) in dichloromethane for the cleavage of their SAC linker, especially since the Fmoc group is stable under these cleavage conditions, but not during the fluoridolysis using TBAF in DMF.<sup>[9, 10]</sup>

The (2-phenyl-2-trimethylsilyl)ethyl(PTMSEL) linker **1** represents a novel anchor for solid-phase peptide synthesis using Fmoc chemistry. It is based on the (2-phenyl-2-trimethylsilyl)ethyl (PTMSE) protecting group<sup>[11]</sup> and renders the liberation of protected, especially Fmoc-protected peptides and glycopeptides in form of the C-terminally free carboxylic acids. In contrast to the SAC linker **2**,<sup>[9]</sup> in the



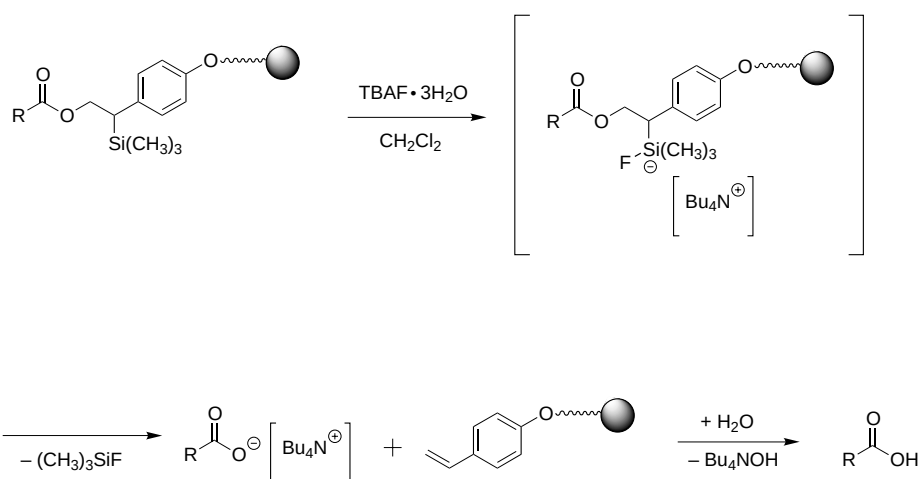
PTMSEL linker not the C–O bond is benzylic and thereby weakened, but the C–Si bond. As a consequence the PTMSEL linker is distinctly more sensitive towards fluoridolysis and more stable towards acidolytic conditions. Thus, its cleavage was achieved with TBAF · 3 H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> under almost neutral conditions (Scheme 1)

To synthesize the PTMSEL linker (Scheme 2), trimethylvinylsilane (**3**) was epoxidized with *m*-chloroperbenzoic acid (mCPBA) to give trimethylsilyloxirane (**4**). Reaction of **4** with lithium di[(*p*-1-ethoxyethoxy)phenyl]cuprate, which is generated in situ by lithiation of 1-(4-bromophenoxy)-1-ethoxyethane with *n*-butyllithium and subsequent reaction with copper(I) iodide, efficiently yields (2-*p*-ethoxyethoxyphenyl-2-trimethylsilyl)ethanol (**5**; 85%). The ethoxyethyl (EE) protecting group is removed in MeOH under catalysis with pyridinium-*p*-toluenesulfonate (PPTS). The PTMSEL linker, (2-*p*-hydroxyphenyl-2-trimethylsilyl)ethanol (**6**), is obtained in a yield of 90% (76% from **4**).

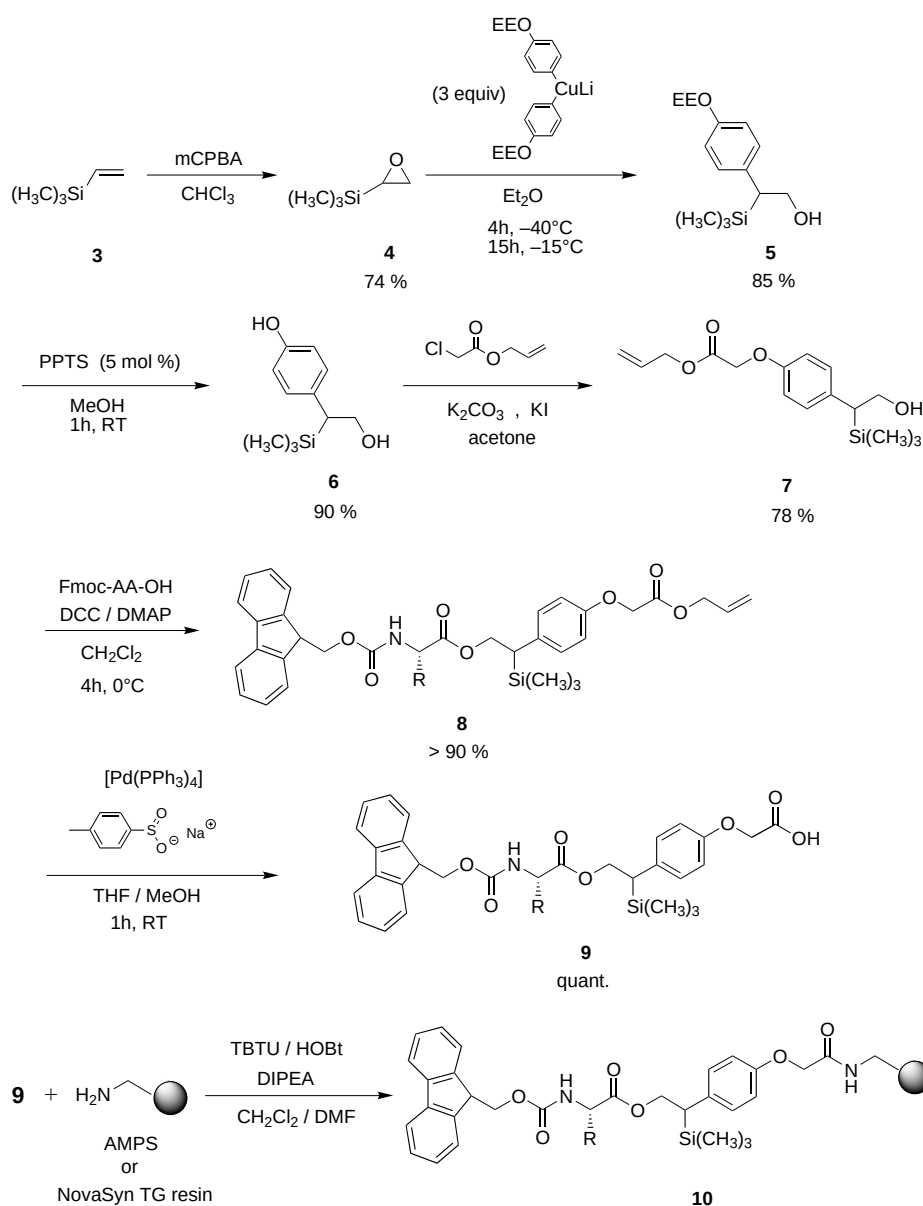
(2-*p*-Hydroxyphenyl-2-trimethylsilyl)ethanol is linked to the polymer support through its phenolic OH group (Scheme 2). The *N*-acyl amino acid is coupled to the linker molecule in solution. Esterification on solid phase is often accompanied by racemization. The alcohol **6** reacts with allyl chloroacetate to give allyl 4-[2-hydroxy-1-(trimethylsilyl)ethyl]phenoxy acetate (**7**). Acylation with the Fmoc-protected amino acid (Fmoc-AA-OH) using dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP)<sup>[12]</sup> gives the allyl ester protected compound **8** (yields: > 90%). The allyl ester of **8** is removed quantitatively by using [Pd(PPh<sub>3</sub>)<sub>4</sub>] and sodium *p*-toluenesulfinate<sup>[13]</sup> or another allyl trapping reagent<sup>[14]</sup> leading to acid **9** (yield ca. 54% over five steps starting from **4**). Acid **9** can be linked to an amino-functionalized resin by using *O*-(benzotriazole-1-yl)-*N,N,N',N'*-tetramethyluroniumtetrafluoroborate (TBTU)/*N*-hydroxybenzotriazole (HOBT)/diisopropylethylamine (DIPEA)<sup>[15]</sup> in DMF/CH<sub>2</sub>Cl<sub>2</sub>. Aminomethylpolystyrene (AMPS; ACT; 200–400 mesh; loading: 1.00 mmol g<sup>-1</sup>) or amino-functionalized TentaGel<sup>[16]</sup> (Nova Syn Tg amino resin;

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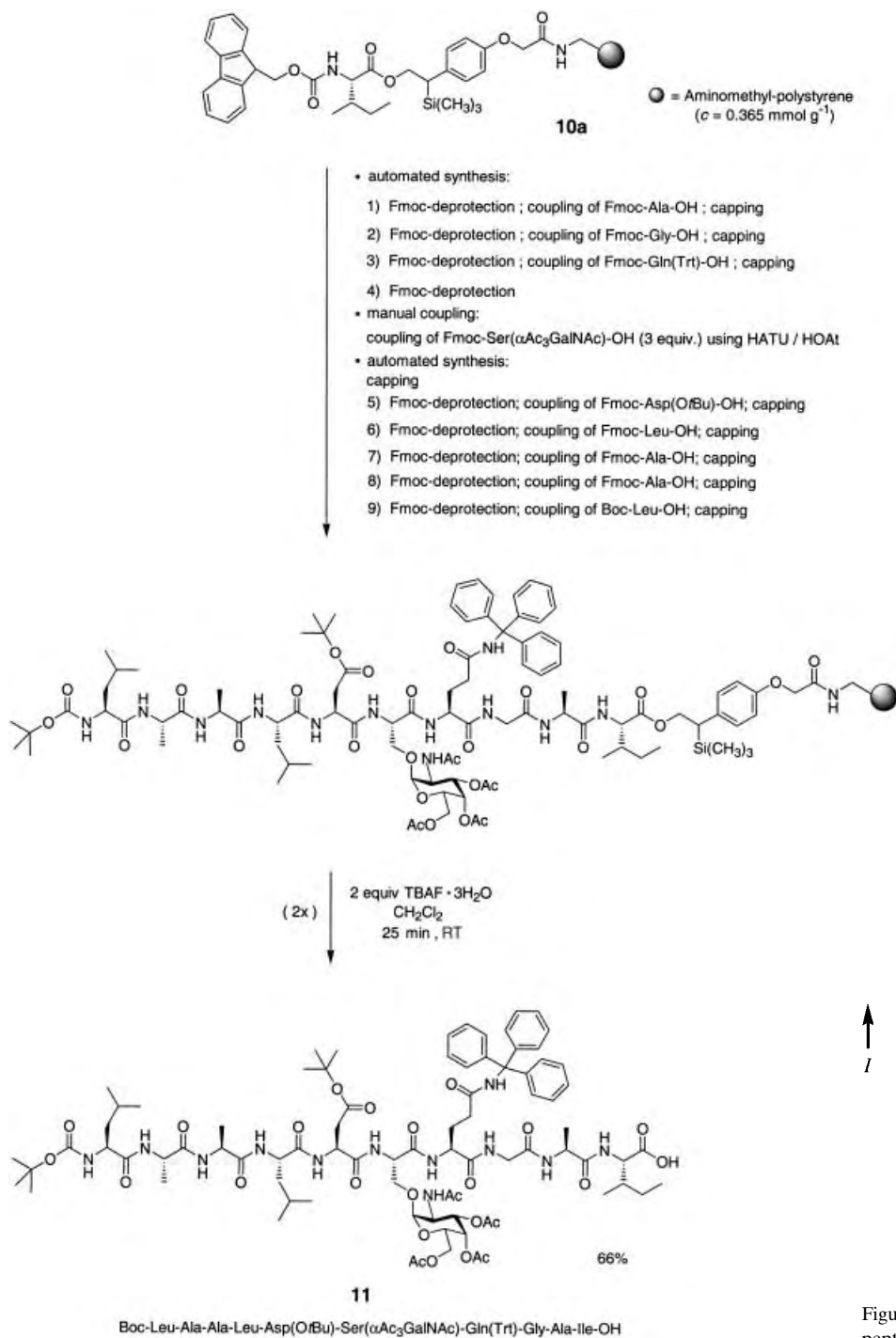
Scheme 1. Fluoride-induced cleavage of the PTMSEL linker.



Scheme 2. Synthesis of the PTMSEL linker and attachment of the first amino acid.

Novabiochem, 110  $\mu\text{m}$  beads, loading: 0.43  $\text{mmol g}^{-1}$ ) were used as polymer supports. Unreacted amino groups were capped with acetanhydride/pyridine (1:3).

The advantageous properties of the PTMSEL linker are demonstrated in the demanding synthesis of a  $\text{T}_\text{N}$ -antigen glycopeptide from the extracellular domain EC1 of LI-cadherin<sup>[17]</sup> (rat), an important cell adhesion protein, which is predominantly found on liver or intestinal cells. Starting from polymer **10a** loaded with Fmoc-Ile-OH (loading: 0.365  $\text{mmol g}^{-1}$ ), glycopeptide Boc-Leu-Ala-Ala-Leu-Asp(OrBu)-Ser( $\alpha\text{Ac}_3\text{GalNAc}$ )-Gln(Trt)-Gly-Ala-Ile-OH (**11**; Boc = *tert*-butoxycarbonyl) was assembled with a peptide synthesizer (Perkin-Elmer ABI 433 A). (Scheme 3) Fmoc deprotections were carried out by up to five four-minute treatments with 30% piperidine in *N*-methylpyrrolidone (NMP) and peptide couplings by reaction with 10 equivalents of Fmoc- or Boc-protected amino acid and coupling reagents (HBTU, HOBT, DIPEA) within 35 minutes. The glycosylated building block Fmoc-Ser( $\alpha\text{Ac}_3\text{GalNAc}$ )-OH<sup>[18]</sup> (3 equiv) was coupled manually using *O*-(7-aza-benzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU)/*N*-hydroxy-7-azabenzotriazole (HOAt).<sup>[19]</sup> After each coupling unreacted amino groups were capped with acetanhydride/DIPEA/HOBT. After completion of the peptide synthesis, the resin was extensively washed with NMP and  $\text{CH}_2\text{Cl}_2$ , which is important because NMP or DMF must be completely removed before cleaving the PTMSEL linker with tetrabutylammonium fluoride. TBAF·3H<sub>2</sub>O is a strong base in polar, aprotic solvents such as DMF, NMP, or THF, but only a weak base (almost neutral) in  $\text{CH}_2\text{Cl}_2$ . The fluoride-induced detachment from the polymer support was achieved manually by shaking the resin with two equivalents of TBAF·3H<sub>2</sub>O (0.2 mmol) in  $\text{CH}_2\text{Cl}_2$  for 25 min.<sup>[20]</sup> Figure 1 shows the chromatogram (HPLC) of crude product **11**, which was obtained after cleavage of the PTMSEL linker.



Scheme 3. Synthesis of a glycodecapeptide from LI-cadherin (rat).

Compounds were identified by HPLC-MS analysis. The major peak (92%) corresponds to the desired product **11**. As side products the aspartimide-containing peptide **12** (2%) and products from various deletion sequences (together  $\approx 4\%$ ) were identified.  $\beta$ -Elimination at the glycosylated serine building block or deacetylation were not observed. Purification was performed by preparative HPLC, which gave glycodecapeptide **11** in 66% yield with respect to the loading of the polymer **10a**.<sup>[21]</sup> Two properties are remarkable: a) In contrast to other linkers, which need to be cleaved with TBAF in DMF, NMP, or THF, side reactions such as the formation of

aspartimides or rearranged aspartyl peptides are extensively suppressed during the mild cleavage of the PTMSEL linker. (During the incomplete cleavage of the SAC linker **2** with benzyltrimethylammonium hydrogen difluoride (BTAHF), aspartimide formation is also suppressed.<sup>[9]</sup> But it is not clear, whether this "super acid labile" linker (1% TFA in  $\text{CH}_2\text{Cl}_2$ ) is cleaved by fluoride and not by the half-neutralized hydrofluoric acid.) b) During the cleavage of the PTMSEL linker most of the common protecting groups in peptide chemistry (even Fmoc, see Scheme 4) and also base-labile glycosidic bonds and protecting groups in glycopeptide syntheses remain stable. Thus, protected glycopeptides can be detached from solid phase and directly used for fragment condensations.

The PTMSEL linker is sterically so demanding that during the removal of the Fmoc group no loss of the polymer-bound dipeptide occurred. Such side reactions often take place in Pro-Pro-linker-, Tyr-Pro-linker-

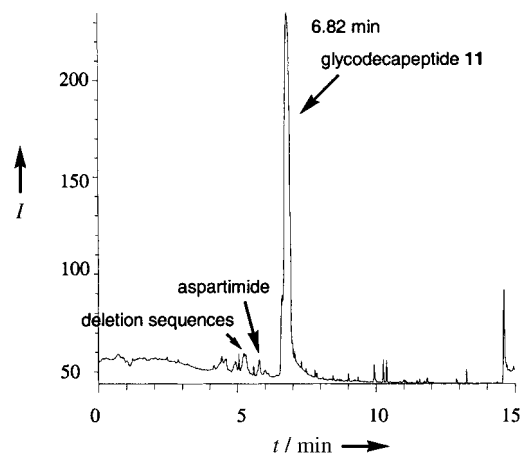
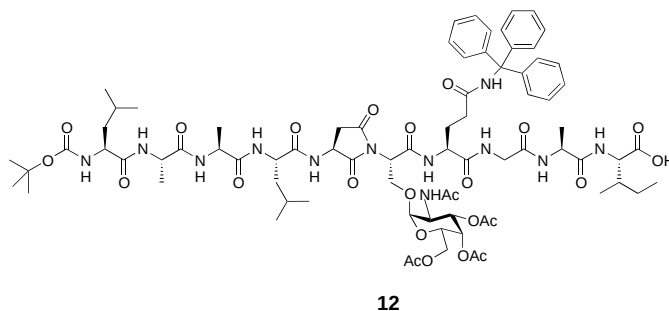
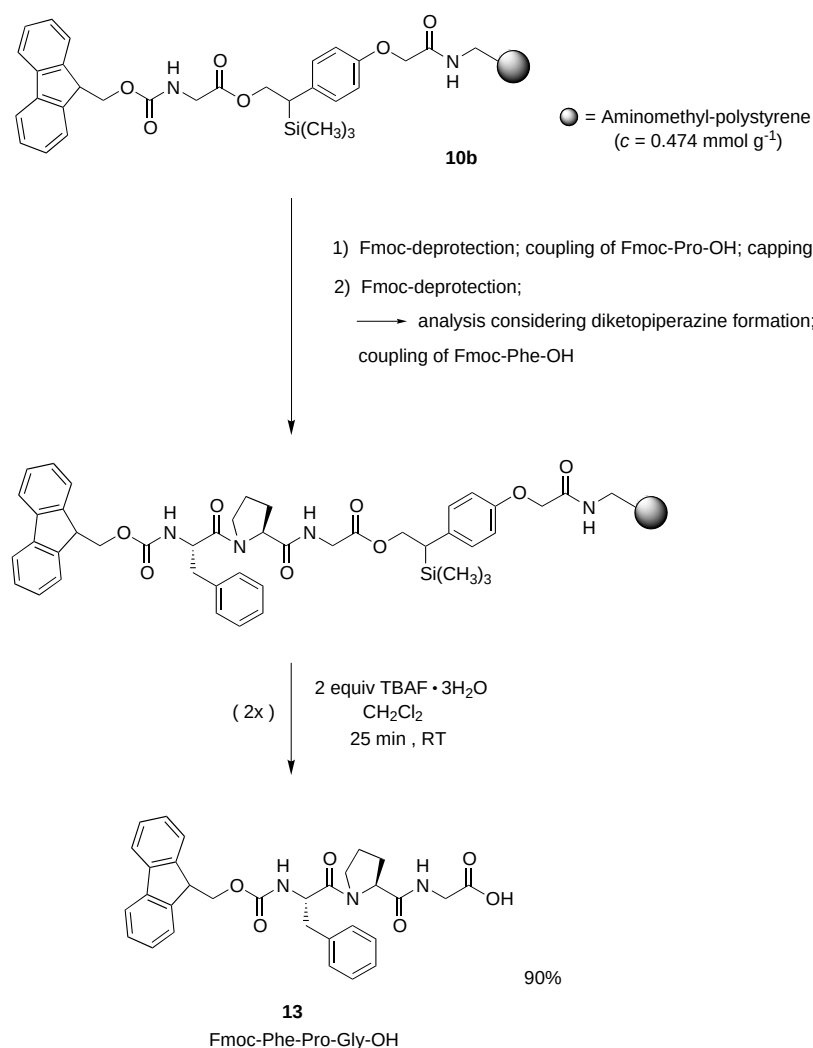


Figure 1. Chromatogram (HPLC) of the crude glycodecapeptide **11** directly after cleavage from the solid support.<sup>[21]</sup>





Scheme 4. Synthesis of a Fmoc-protected tripeptide containing a Pro-Gly sequence, usually prone to diketopiperazine formation.

and Pro-Gly-linker-sequences. The solid-phase synthesis of tripeptide Fmoc-Phe-Pro-Gly-OH (**13**) is shown in Scheme 4. Even for this sequence, diketopiperazine formation was not observed, which was proven by loading analysis after each coupling as well as by HPLC-MS analysis of the filtrate obtained from the Fmoc deprotection from the second amino acid (Pro). Usual column chromatography gave the desired *N*-terminal Fmoc-protected tripeptide **13** in 90 % yield with respect to the loading of **10b**.

Thus, the PTMSEL linker is particularly useful for the solid-phase synthesis of protected peptides and glycopeptides using Fmoc chemistry. Release from the solid support is simply achieved without expensive chemicals, yielding almost pure peptides. Most of the common protecting groups (Fmoc, Boc, benzyloxycarbonyl (Z), allyloxycarbonyl (Aloc), *tert*-butyl, benzyl, allyl, trityl, acetyl, etc.) are stable under the mild cleavage conditions of the PTMSEL linker, thus providing the possibility of orthogonal, three-dimensional protecting group strategies. Aspartimide formation, which is often a problem in solid-phase peptide synthesis, is decisively suppressed. With base-labile *O*-glycopeptides, side reactions do not take place. The new linker is sterically so demanding that diketopiper-

azine formation at the stage of the polymer-bound dipeptide is prevented.

Solid-phase synthesis using Boc chemistry is not possible, because the PTMSEL linker is cleaved by treatment with TFA. This lability has already been described for the PTMSE-protecting group.<sup>[11]</sup>

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- [20] Cleavage procedure: The resin was shaken with two equivalents of TBAF · 3H<sub>2</sub>O (0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) for 25 min. After filtration, the resin was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). Combined filtrates were extracted with H<sub>2</sub>O (10 mL) to remove remaining fluoride. The cleavage protocol was repeated with TBAF · 3H<sub>2</sub>O (ca. 0.7 equiv, 0.07 mmol, 2 equiv with respect to the residual product on the resin). The combined CH<sub>2</sub>Cl<sub>2</sub> solutions were washed twice with

water, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The protected peptide was obtained in an almost pure form.

- [21]  $R_t = 6.82$  min (Luna C18-2/75  $\times$  4.6 mm, 3  $\mu\text{m}$ , 1  $\text{mL min}^{-1}$ ; A:  $\text{H}_2\text{O}$ , B:  $\text{CH}_3\text{CN}$ ; 0–0.75 min: 20% B in A, 0.75–10 min: 20% B in A to 100% B, 10–12.5 min: 100% B, 12.5–13.5 min: 100% B to 20% B in A, 13.5–15 min: 20% B in A);  $[\alpha]_D^{25} = 1.96$  ( $c = 0.90$  in  $\text{MeOH}$ );  $^1\text{H NMR}$  (400 MHz,  $[\text{D}_6]\text{DMSO}$ ,  $^1\text{H}, ^1\text{H-COSY}$ ):  $\delta = 8.53$  ( $s_b$ , 1H;  $\omega\text{-NH Q}$ ); 8.08–8.14 (m, 3H; NH D, S, A); 7.85–7.98 (m, 5H; NH 2  $\times$  A, Q, L, G); 7.61 (d, 1H; NH GalNAc,  $J = 8.6$  Hz); 7.14–7.26 (m, 15H; Trt); 6.85 (d, 1H; NH-urethane, L,  $J = 7.43$  Hz); 5.28 (s, 1H; H-4'); 5.00 (dd, 1H; H-3',  $J_{\text{H3,H4}} = 2.74$  Hz,  $J_{\text{H3,H2}} = 11.74$  Hz); 4.85 (d, 1H; H-1',  $J_{\text{H1,H2}} = 3.13$  Hz); 4.56–4.64 (m, 1H; D $^a$ ); 4.47–4.52 (m, 1H; S $^a$ ); 3.94–4.40 (m, 9H; 3  $\times$  A $^a$ , I $^a$ , Q $^a$ , L $^a$ , H-2', H-5', H-6'); 3.88–3.92 (m, 2H; L $^a$ , H-6'); 3.72–3.76 (m, 2H; G $^a$ ); 3.60–3.64 (m, 2H; S $^b$ ); 2.71–2.73 (m, 1H; D $^b$ ); 2.45–2.49 (m, 1H; D $^b$ ); 2.32–2.38 (m, 2H; Q $^b$ ); 2.07 (s, 3H;  $\text{CH}_3$  NHAc); 1.71–1.94 (m, 12H; 3  $\times$   $\text{CH}_3$  OAc, I $^b$ , Q $^b$ ); 1.52–1.59 (m, 2H; L $^b$ ); 1.36 (s, 9H; 3  $\times$   $\text{CH}_3$  Boc); 1.33 (s, 9H; 3  $\times$   $\text{CH}_3$  *t*Bu);

1.33–1.42 (m, 5H; 2  $\times$  L $^b$ , I $^b$ ); 1.11–1.18 (m, 10H; 3  $\times$  A $^b$ , I $^b$ ); 0.79–0.86 (m, 18H; 4  $\times$  L $^b$ , I $^b$ , I $^b$ );  $^{13}\text{C NMR}$  (100.6 MHz,  $[\text{D}_6]\text{DMSO}$ , broad band, DEPT):  $\delta = 172.86, 172.69, 172.18, 172.11, 172.02, 171.53, 170.39, 170.19, 170.04, 169.97, 169.91, 169.71, 169.34, 169.05, 168.22, 168.11, 156.03$  (C=O); 145.00 (C $_{\text{ipso}}$ -Trt); 128.61 (C $_{\text{para}}$ -Trt); 127.54 (C $_{\text{ortho}}$ -Trt); 126.41 (C $_{\text{meta}}$ -Trt); 97.29 (C-1'); 80.39 (C $_{\text{quart}}$  Boc); 78.34 (C $_{\text{quart}}$  *t*Bu); 69.37 (C $_{\text{quart}}$  Trt); 67.51 (C-3'); 66.96 (S $^b$ ); 66.83 (C-4'); 65.92 (C-5'); 61.14 (C-6'); 56.04 (I $^a$ ); 52.66, 52.39, 52.20 (2  $\times$  L $^a$ , S $^a$ ); 50.87, 49.28, 48.08, 47.95, 47.59, 46.57 (D $^a$ , Q $^a$ , 3  $\times$  A $^a$ , C-2'); 41.61 (G $^a$ ); 40.37, 40.22 (2  $\times$  L $^b$ ); 36.92 (D $^b$ ); 36.08 (I $^b$ ); 32.39 (Q $^b$ ); 27.89 (3  $\times$   $\text{CH}_3$  Boc); 27.66 (Q $^b$ ); 27.37 (3  $\times$   $\text{CH}_3$  *t*Bu); 24.46 (I $^b$ ); 23.94, 23.82 (2  $\times$  L $^b$ ); 22.69, 22.33, 21.21, 20.22 (4  $\times$   $\text{CH}_3$  acetyl); 20.18, 20.13 (4  $\times$  L $^b$ ); 18.05, 17.67, 17.38 (3  $\times$  A $^b$ ); 15.24 (I $^b$ ); 11.08 (I $^b$ ); MALDI-TOF-MS ( $\alpha$ -cyanocinnamic acid matrix, positive-ion mode):  $m/z$ : 1709.3  $[\text{M}+\text{Na}]^+$ , 1725.2  $[\text{M}+\text{K}]^+$ , 1731.3  $[\text{M}+2\text{Na}]^+$ .

# Unprecedented Ferromagnetic Interaction in Homobinuclear Erbium and Gadolinium Complexes: Structural and Magnetic Studies

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Recent papers have shown that the interaction between a gadolinium ion and a second spin carrier (M) is not compulsorily ferromagnetic as suggested earlier for the complexes in which M is an organic radical<sup>[1, 2]</sup> or a metal ion (Cu<sup>2+</sup>,<sup>[3, 4]</sup> VO<sup>2+</sup><sup>[5]</sup>). Moreover, little attention has been paid to the fact that the Gd⋯Gd interaction, which is a particular case of Gd⋯M interactions, was found to be antiferromagnetic in all the complexes reported by now.<sup>[6–11]</sup> It should be noted that the number of di- and polynuclear gadolinium compounds for which structural and magnetic data are available is restricted<sup>[12]</sup> and that the factors governing the nature and magnitude of the Gd⋯Gd interaction have not been clarified. Here we report two lanthanide(III) dimers—namely [LnL<sub>3</sub>(H<sub>2</sub>O)<sub>n</sub>]<sub>2</sub>·xH<sub>2</sub>O with Ln = Er (**1**; n = 2, x = 4) and Gd (**2**; n = 1, x = 0), and HL = salicylic acid—that display an unprecedented ferromagnetic behavior. Well-shaped crystals of **1** have been obtained, which allows a structural study to be performed.<sup>[14]</sup>

The molecular structure of **1** is shown in Figure 1. Obviously the molecular entity is binuclear and possesses an inversion center while the previously published lanthanide salicylate complexes are polynuclear.<sup>[15–17]</sup> Of the six salicylate anions, four are acting as bridging ligands through their carboxylato groups; two function in the usual  $\eta^1:\eta^1:\mu_2$  mode whereas the

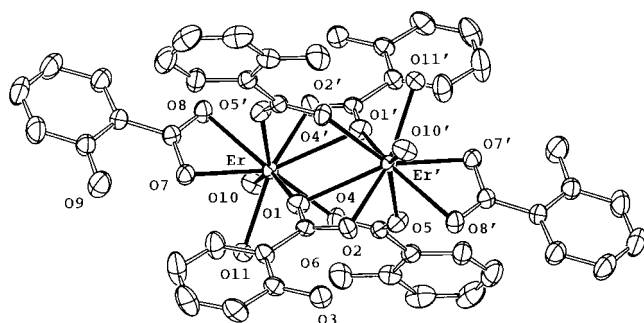


Figure 1. Ortep plot of **1** (thermal ellipsoids for 50% probability). Hydrogen atoms are omitted. Selected bond lengths [Å]: Er-O1 2.282(2), Er-O2' 2.353(2), Er-O5' 2.329(2), Er-O8 2.492(2), Er-O11 2.377(2), Er-O4 2.349(2), Er-O1' 2.724(2), Er-O7 2.354(2), Er-O10 2.360(2), Er'-O1 2.724(2), Er'-O2 2.353(2), Er'-O5 2.329(2).

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two other bridge in the less common  $\eta^2:\eta^1:\mu_2$  fashion.<sup>[18]</sup> In the latter case one oxygen atom (O2, O2') is terminally bound to the related erbium ions (Er, Er') and the second oxygen (O1, O1') is involved in a monoatomic bridge between the two lanthanide ions. Each of the two remaining anions chelates a metal ion (Er and Er'). As a result of the inversion center the Er(O1, O1')Er' double bridging network is perfectly planar. The second bridge through the atoms O4, Er, O5', O4', Er', and O5 is not planar. The dihedral angle between the two planes Er(O1, O1')Er' and Er(O4, O4')Er' is equal to 81.58(4)° whereas the erbium ions are separated by 4.0093(2) Å. The coordination of each lanthanide ion is completed to nine by two water molecules and one bidentate chelating carboxylato group. It should be noted that the phenolic OH function of the ligand is not involved in any coordination sphere. The bridging network present in **1** is original for salicylate bridges but not unprecedented if we consider the acetate bridges. An almost identical core has yet been observed in the structure of [Ce<sub>2</sub>(CH<sub>3</sub>COO)<sub>6</sub>(bipy)<sub>2</sub>]<sup>[6]</sup> (bipy = 2,2'-bipyridine) and extended to the related gadolinium complex (these complexes are numbered **3** and **4**, respectively, in the following text). The dinuclear units are well isolated from each other, with intermolecular distances greater than 6 Å.

As we have not succeeded in obtaining crystals of **2**, a wide-angle X-ray scattering study (WAXS) has been performed to check the similarity of the structures **1** and **2**. Indeed a comparison of the experimental RDF for **2** and the calculated one for **1**, extracted from the WAXS data (Figure S3, Supplementary Material) clearly shows that a very good agreement is obtained for distances lower than 8 Å. As an example, the Ln⋯Ln distance, equal to 4.00 Å in **1**, is now equal to 4.25 Å in **2**, as a result of the lanthanide contraction on going from the lighter to the heavier Ln ions. The difference appearing beyond 8 Å suggests that the two complexes are not isostructural. This is not really surprising if we remember that the number of water molecules linked to the Ln center is different for **1** and **2** (two for **1** and one for **2**). Nevertheless, this study confirms the dimeric structure of the gadolinium complex **2**.

The thermal variation of the  $\chi_M T$  product ( $\chi_M$  = molar magnetic susceptibility) for **1** is shown in Figure 2. At 300 K,  $\chi_M T$  is equal to 22.2 cm<sup>3</sup> mol<sup>-1</sup> K which is the value expected for two magnetically insulated Er<sup>3+</sup> ions in the <sup>4</sup>I<sub>15/2</sub> ground state. As the temperature is lowered,  $\chi_M T$  decreases down to 4 K. At that temperature, it reaches a minimum of 12.0 cm<sup>3</sup> mol<sup>-1</sup> K and then increases as  $T$  is further lowered.

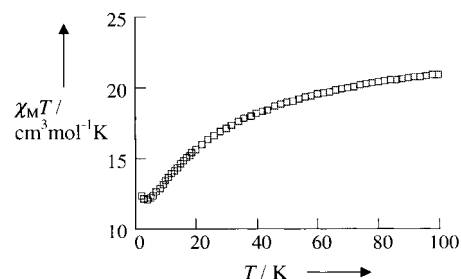


Figure 2. Temperature dependence of  $\chi_M T$  for **1** at 0.1 T.

The decrease in  $\chi_M T$  undoubtedly originates in the thermal depopulation of the highest Stark components resulting from the splitting of the free ion ground state  $^4I_{15/2}$  by the crystal field. The profile of the  $\chi_M T$  vs.  $T$  curve at low temperature indicates that the effects of the depopulation of the Stark levels conflict with an antagonist process. In keeping with the structural data, this additional process must be an intra-molecular ferromagnetic interaction between the lanthanide ions, both of which are most probably in a local ground Kramers doublet state. As noticed above, intermolecular interactions have to be excluded because the dinuclear units are well isolated from each other. Furthermore, there is no pathway to transmit a magnetic interaction between these dinuclear units.

This situation is simpler in the case of **2** since  $Gd^{3+}$  has an  $^8S_{7/2}$  ground state without first-order orbital momentum. At 300 K,  $\chi_M T$  (Figure 3) is equal to  $15.7 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$  which is the

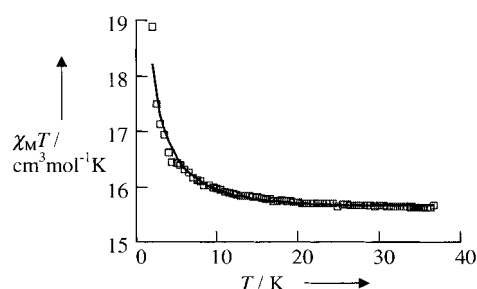


Figure 3. Temperature dependence of  $\chi_M T$  for **2** at 0.1 T. The solid line represents the best fit (see text).

value attributable to two noninteracting spin carriers, each being characterized by  $S=7/2$  and  $g=2.0$ . Lowering the temperature causes  $\chi_M T$  to increase. A value of  $18.9 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$  is reached at 2 K. Fitting the experimental data to the equation<sup>[6]</sup> deduced from the isotropic spin Hamiltonian  $\mathcal{H} = -J S_{Gd1} S_{Gd2}$  yields  $J=0.05 \text{ cm}^{-1}$  and  $g=1.98$ , with an agreement factor  $R$  equal to  $2.0 \cdot 10^{-3}$  ( $R = \Sigma[(\chi_M T)_{\text{obs}} - (\chi_M T)_{\text{calc}}]^2 / \Sigma[(\chi_M T)_{\text{obs}}]^2$ ). The unexpected ferromagnetic nature of the  $Gd \cdots Gd$  interaction is further supported by magnetization measurements in the 0–5 T range at 2 K (Figure 4). The experimental values of  $M$  are

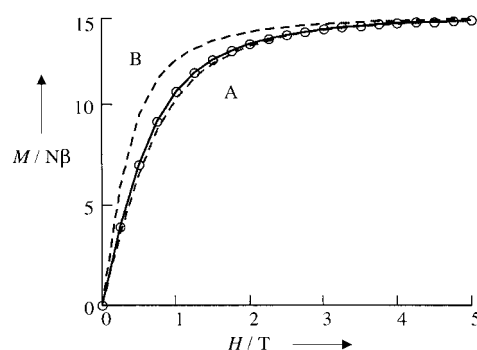


Figure 4. Field-dependent magnetization of **2** at 2 K (circles). The solid line corresponds to the Brillouin function for the parameters extracted from the static susceptibility data (see text) and the dashed lines represent the Brillouin function for (A) two uncoupled Gd centers and (B) an  $S=7$  state.

fairly well reproduced by the Brillouin function that corresponds to the parameters extracted from the static susceptibility data (Figure 4, full line). In addition, this line is comprised in between the two dashed lines that correspond to (A) two uncoupled Gd centers and (B) to a  $S=7$  state, which confirms the weak ferromagnetic correlation between the two gadolinium ions. This conclusion contrasts with previous findings which unanimously document the occurrence of an antiferromagnetic ground state in homopolynuclear gadolinium complexes,<sup>[6–12]</sup> in which the coupling constants vary from  $-0.05$  to  $-0.21 \text{ cm}^{-1}$ . The most impressive comparison concerns complexes **2** and **4**. Although both complexes are bridged by carboxylato groups, the two gadolinium ions do present opposite magnetic interactions. At that stage, that is, without structural determinations, we cannot indicate which structural differences are responsible for the sign reversal of the interaction. A similar situation has been reported for (Cu, Gd)<sup>[3, 4]</sup> and (VO, Gd)<sup>[5]</sup> complexes, which suggests that in all these species the observed coupling results from a delicate balance between two contributions of opposite signs and slightly different magnitudes. Work is in progress to design and characterize new examples of ferromagnetic  $Gd \cdots Gd$  interactions for a better understanding of the interaction mechanism.

#### Experimental Section

All starting materials were purchased from Aldrich and were used without further purification. Elemental analyses (C,H,N) were carried out by the Service de Microanalyse du Laboratoire de Chimie de Coordination, Toulouse. Magnetic susceptibility data were collected on powdered samples of the different compounds with a SQUID-based sample magnetometer on a QUANTUM Design Model MPMS instrument. All data were corrected for diamagnetism of the ligands estimated from Pascal's constants.<sup>[19]</sup> Amorphous powder of **2** was sealed in a Lindemann capillary. The scattering diffusion spectrum of the samples irradiated with graphite-monochromatized  $MoK_{\alpha}$  radiation ( $\lambda=0.71069 \text{ \AA}$ ) was obtained using a LASIP diffractometer.<sup>[20]</sup>

**[L<sub>6</sub>Gd<sub>2</sub>] · 2H<sub>2</sub>O:** After stirring a mixture of salicylic acid (1.38 g, 10 mmol) and lithium hydroxide hydrate (0.42 g, 10 mmol) in methanol (40 mL) for ten minutes a solution of gadolinium nitrate  $Gd(NO_3)_3 \cdot 5H_2O$  (1.50 g, 3.4 mmol) dissolved in water (30 mL) was added. The resulting solution was heated and concentrated for 30 minutes to yield a white precipitate. After cooling, the precipitate was filtered off and washed with water/methanol (1:1), acetone, and diethyl ether. Yield: 1.5 g (77%). Anal. calcd for  $C_{42}H_{34}Gd_2O_{20}$ : C 43.0, H 2.9, Gd 26.8; found: C 42.6, H 2.7, Gd 26.7.

**[L<sub>6</sub>Er<sub>2</sub>] · 8H<sub>2</sub>O:** This compound was prepared following the experimental procedure described above. Yield: 1.0 g (48%). Anal. calcd for  $C_{42}H_{46}Er_2O_{26}$ : C 38.8, H 3.6, Er 25.7; found: C 38.6, H 3.4. In another experiment, the mother solution was set aside. Three days later, crystals suitable for X-ray analysis could be isolated.

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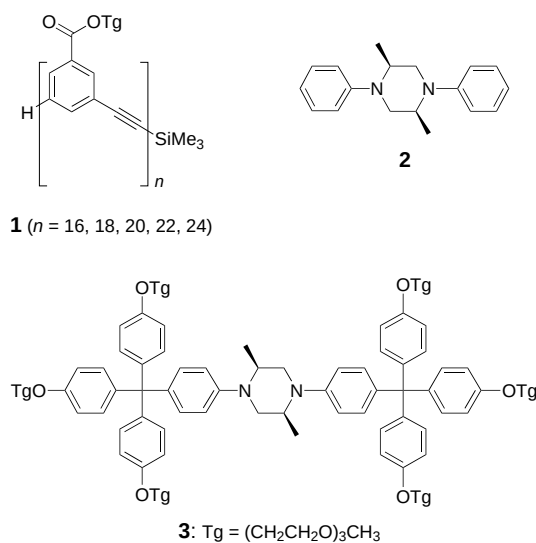


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## Foldamers as Dynamic Receptors: Probing the Mechanism of Molecular Association between Helical Oligomers and Rodlike Ligands\*\*

Aya Tanatani, Thomas S. Hughes, and Jeffrey S. Moore\*

The helix is one of the most significant structural motifs observed in biological<sup>[1]</sup> and synthetic<sup>[2]</sup> polymers. We have previously shown that *m*-phenylene ethynylene oligomers **1** exhibit unique helical structures in polar solvents<sup>[3]</sup> and possess a cavity which can bind hydrophobic molecules.<sup>[4]</sup> The rodlike ligand **2** exhibited affinities to **1** that were dependent on either the length of the oligomer or the height



of the helical cavity. The association constants rose steadily as the length of the oligomer increased from the decamer to the octadecamer but then reached a plateau, with a weak maximum at the icosamer. Only nonspecific, nondirectional solvophobic interactions stabilize these complexes.

Intuitively, a capped rod, namely, a dumbbell-shaped ligand, may exhibit greater specificity by blocking the strong binding of oligomers which are too long to fit between the caps. However, the ability of capped rods to function as ligands depends on the presence of a kinetically accessible complexation pathway. Two possible limiting mechanisms can be imagined in a polar solvent that favors the folded state of **1**:

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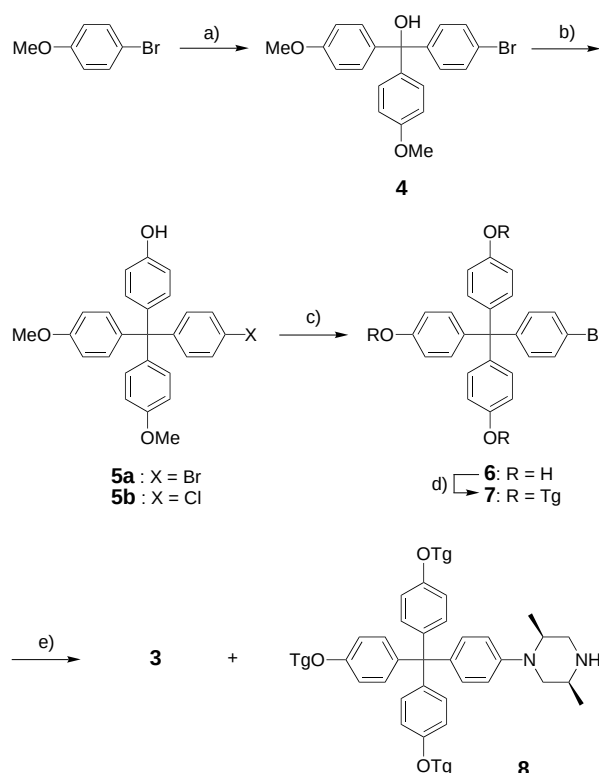
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1) the chiral ligand threads into the helical cavity of a rigid oligomer, or 2) a transiently unfolded oligomer winds around the chiral ligand (Figure 1a). This mechanistic question parallels that asked of many biological systems; that is, how much reorganization of the folded receptor occurs upon binding?<sup>[5]</sup> Here, we describe the high affinity and high specificity of a dumbbell-shaped ligand, whose shape should mimic the mode of binding of **2** to **1** and restrict the possible mechanisms of complexation.

The dumbbell-shaped ligand **3** consists of *N,N'*-diphenylpiperazine **2** capped with triarylmethyl moieties at both ends of the rod. Each terminal aryl group was *para* substituted with triglyme (Tg) ethers to improve solubility. The ends of this molecule should be too bulky to enter the cavity of a rigid helical oligomer by threading (Figure 1b).<sup>[6]</sup> This assumption was evaluated by molecular modeling; structures of the ligand and helical oligomer were optimized by molecular mechanics.<sup>[7]</sup> The diameter of the helical cavity was calculated to be 8.7 Å, while the diameter of the capping group (without side chains) was calculated to be 10.2 Å. By comparison, the diameter of the piperazine portion of the ligand was about 6.6 Å. Therefore, the observation of a high binding affinity between **3** and oligomer **1** would suggest that a dynamic mechanism such as pathway (2) (Figure 1a) is viable.

The synthesis of dumbbell-shaped molecule **3** is illustrated in Scheme 1. Triarylmethanol **4** was prepared in 72 % yield by the reaction of methyl 4-bromobenzoate with *p*-methoxyphenylmagnesium bromide. Bis(tetraarylmethane) **5a** was obtained in 50 % yield by treatment of **4** in phenol with a catalytic amount of HBr according to the procedure reported by Gibson et al.<sup>[8]</sup> It should be noted that the use of a catalytic amount of HCl resulted in a 1:1 mixture of **5a** and **5b**. After removal of the methyl groups by treatment with BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (93 % yield), etherification of **6** with triglyme under Mitsunobu conditions<sup>[9]</sup> gave **7** in 47 % yield. Buchwald–Hartwig amination of **7** with (2*S*,5*S*)-2,5-dimethylpiperazine afforded the monoadduct **8** (45 % yield) and target **3**, albeit in low yield (10 %). No epimerization of the piperazine ring was observed during amination.



Scheme 1. Synthesis of dumbbell-shaped ligand **3**: a) Mg, diethyl ether, 40 °C, 12 h; methyl 4-bromobenzoate, 40 °C, 18 h, 72 %; b) phenol, HBr, 120 °C, 16 h, 50 %; c) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h, 93 %; d) CH<sub>3</sub>(OCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>OH, diethylazodicarboxylate, Ph<sub>3</sub>P, THF, RT, 18 h, 47 %; e) [Pd<sub>2</sub>(dba)<sub>3</sub>], NaO-*t*Bu, 2-diphenylphosphanyl-2'-dimethylaminobiphenyl, *cis*-(2*S*,5*S*)-2,5-dimethylpiperazine, toluene, 85 °C, 18 h, 10 % of **3**. dba = dibenzylideneacetone.

Induced circular dichroism (CD) signals were observed upon mixing solutions of **3** and the members of oligomer series **1** (*n* = 16, 18, 20, 22, 24), which indicates that the presence of the capping groups did not prevent association. Figure 2 (inset) shows a representative series of spectra obtained from the addition of different concentrations of

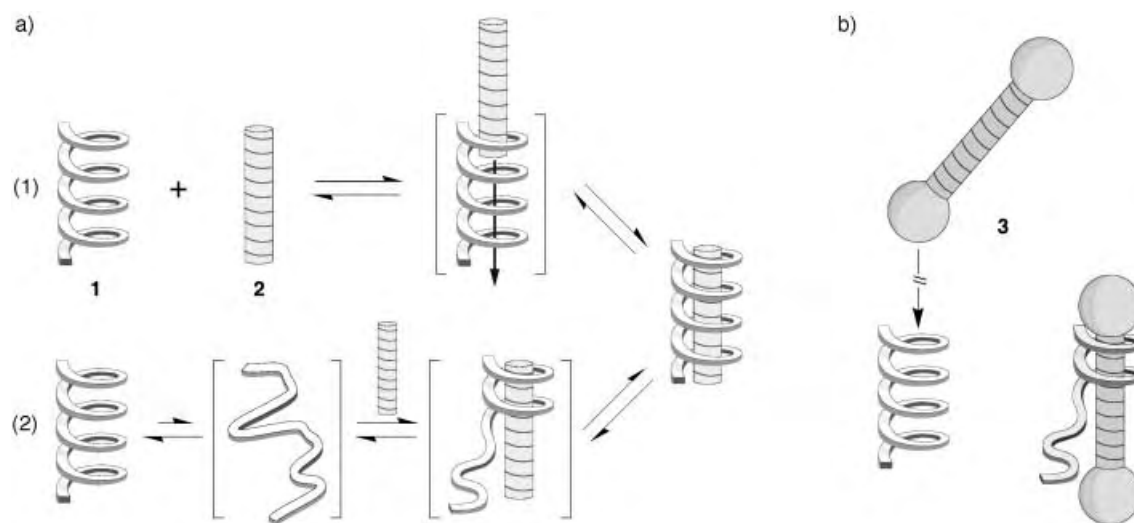


Figure 1. Foldamer association with rodlike ligands. a) Two possible limiting mechanisms are the static, rigid case in which the chiral ligand threads through the cavity of the helical oligomer without disruption of the helical structure (1), and the dynamic, flexible case in which the unfolded or partially folded oligomer winds around the chiral ligand (2). b) Mechanistic probe.

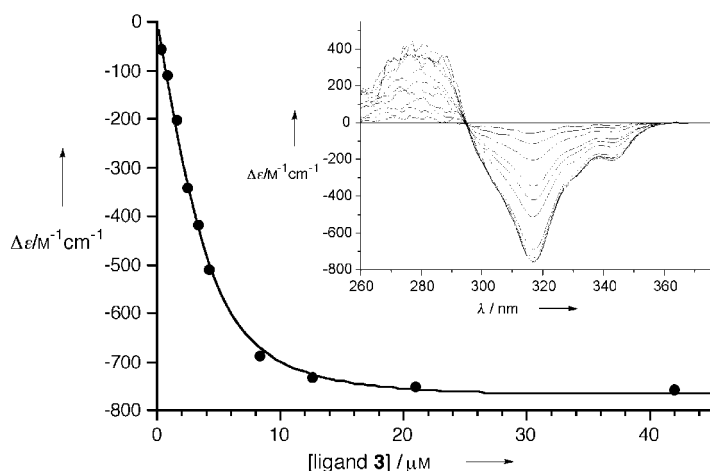


Figure 2. Plot of the  $\Delta\epsilon$  value at 317 nm against the concentration of ligand **3** for its association with oligomer **1** ( $n=20$ ) in 40%  $\text{H}_2\text{O}$  in  $\text{CH}_3\text{CN}$  at  $294 \pm 1$  K.  $[\mathbf{1}] = 4.2 \mu\text{M}$ . The points represent the observed data, while the line represents the nonlinear least-squares fit. The inset shows the corresponding CD spectra.

enantiomerically pure **3** to the icosamer in 40% aqueous acetonitrile. The CD spectra were very similar to those observed for the 1:1 complex formed between **2** and **1**,<sup>[4b]</sup> and the stoichiometry of the complex formed between **3** and **1** was also determined to be 1:1 from the quality of the nonlinear least-squares fitting to the 1:1 binding isotherm.<sup>[10][11]</sup>

The binding affinities of **3** for members of oligomer series **1** were determined by these nonlinear fits.<sup>[12]</sup> As shown in Figure 3, the value of the association constant  $K_{11}$  increased as the length of the oligomer increased from the hexadecamer to the docosamer.<sup>[13]</sup> The length dependence of the association constants and the similarity of the CD spectra to those observed previously for the 1:1 complex formed between **2** and **1** suggest that dumbbell-shaped ligand **3** also binds within the helical cavity of the folded oligomer rather than in some alternative geometry, such as transversely through the turns of the helix or to a nonhelical conformation. The  $K_{11}$  value of **3** with the icosamer of **1**<sup>[14]</sup> was calculated to be  $(1.0 \pm 0.1) \times 10^6 \text{ M}^{-1}$ . This value is more than 20 times stronger than the  $K_{11}$  value of **2** with the icosamer. Not only is the affinity of **1** for ligand **3** larger than that of ligand **2** at each oligomer length, the specificity of ligand **3** towards oligomers of different lengths is also much greater than that of ligand **2**.<sup>[15]</sup> For example, in the case of rodlike ligand **2**, the association of the icosamer is only 2.3 times larger than that of the hexadecamer. However, this ratio is about 20:1 for dumbbell-shaped ligand **3**. This specificity can easily be seen in Figure 3; the maximum in the plot of the  $K_{11}$  value versus oligomer length is much more pronounced for **3** than for **2**.

We previously assumed that the affinity depends on the area of contact between the interacting molecular surfaces, given the absence of any obvious, specific, directional interactions.<sup>[4b]</sup> The predicted enthalpy of binding from molecular mechanics models<sup>[16]</sup> increased nearly linearly as the oligomer increased in size from the hexadecamer to the docosamer, but decreased for the tetracosamer. Just as for the **1**·**2** complexes, no specific intermolecular interactions were evident in the modeled **1**·**3** complexes, with the exception of possible

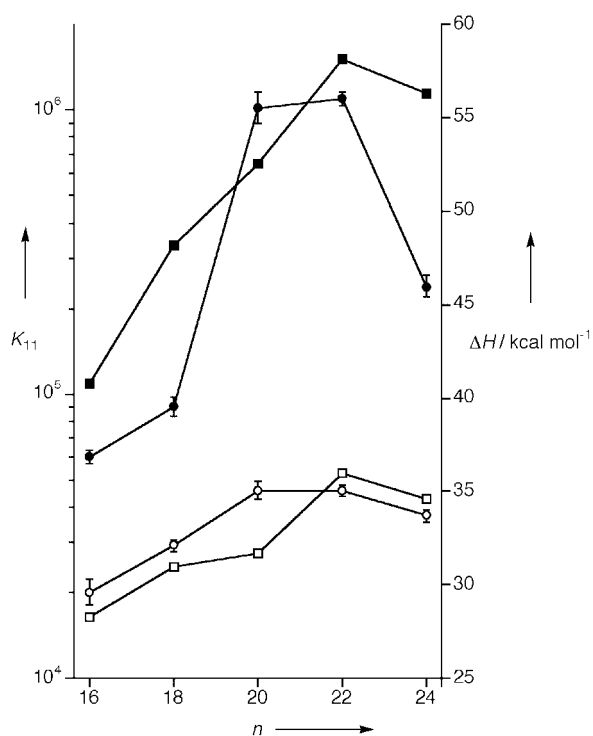


Figure 3. Plot of  $\log K_{11}$  values (circles) and modeled heat of association (squares) against oligomer length for ligands **2** and **3**. Experimental  $K_{11}$  values for **2** ( $\circ$ ) are taken from ref. [4b] for direct comparison to **3** ( $\bullet$ ). All measurements were recorded in a mixed solvent of 40%  $\text{H}_2\text{O}$  in  $\text{CH}_3\text{CN}$  at  $294 \pm 1$  K.  $[\mathbf{1}] = 4.2 \mu\text{M}$ .  $\square$  represents the calculated heat of association for **2** and  $\blacksquare$  for **3**. The energy scale is arbitrary since no contribution from the entropy of binding is included.

aromatic–aromatic interactions between the terminal oligomeric phenyl rings and the phenyl rings of the trityl capping group. The modeled structures of all of the complexes **1**( $n=16-20$ )·**3** revealed the ligand could be encapsulated within a completely helical oligomer, whereas the **1**( $n=24$ )·**3** complex could only form upon some twisting of the terminal oligomeric phenyl groups out of the ideal helical conformation. The fully folded hexadecamer and octadecamer are too short to interact with both of the capping groups; the affinity is thus relatively low and the specificity for these lengths not very high. However, the icosamer and docosamer are long enough to potentially form energetically favorable contacts with both tetraarylmethane capping groups. These stabilizing interactions may be responsible for the large differences between the  $K_{11}$  values of ligands **2** and **3**, and the high chain length specificity. The lower binding constant for the tetracosamer, as well as the perturbation of the helical structure of the oligomer in the model of the **1**( $n=24$ )·**3** complex suggests that the helix may be too long to fit between the capping groups in its fully folded state. It is possible that some deformation occurs to accommodate **3**, such as alteration of the pitch of the helix or fraying of the helix ends as seen in the model.

The kinetics of the association of **1** with **2** and with **3** were examined to further probe the mechanism of complexation. As can be seen in Figure 4, the diastereomeric excess of the **1**( $n=20$ )·**2** complex is already present by the time the first measurement is made at 60 seconds after mixing, and does not

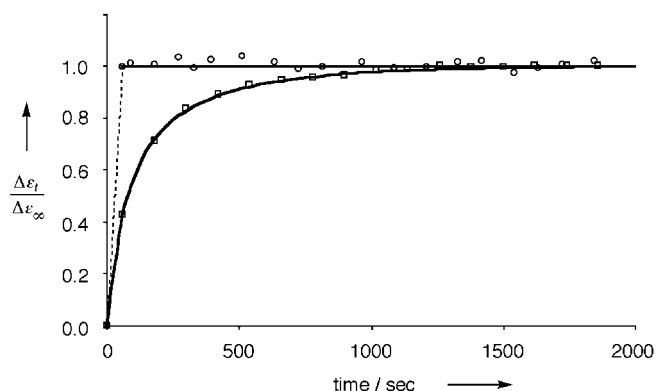


Figure 4. Kinetics of complexation of **2** and **3** with **1**. The percentage of the equilibrium signal is shown as a function of the time after mixing the ligand and the oligomer.  $\square$  represents the formation of the complex of **3** with **1** while  $\circ$  represents the complex of **2** with **1**. The solid lines are nonlinear fits to the data using a second-order kinetic model. The dashed line indicates the absence of data for very short reaction times; the shape of the kinetic curve in this region is undetermined.  $[\mathbf{1}] = 4 \mu\text{M}$ ,  $[\mathbf{2}] = 45 \mu\text{M}$ ,  $[\mathbf{3}] = 10 \mu\text{M}$  in 40%  $\text{H}_2\text{O}$  in  $\text{CH}_3\text{CN}$ .

change appreciably over the next thirty minutes. This observation suggests that the binding event is rapid, as is possible for a direct threading mechanism such as pathway (1) in Figure 1. Different kinetic behavior is observed for the association of **1** and **3**.

The growth of the CD signal was slower for the association of **1** with **3** (Figure 4). It is reasonable to assume that the slower establishment of the diastereomeric equilibrium is the result of the greater degree of oligomer chain reorganization required to accommodate ligand **3** within the helical cavity. The transition state for this association would be both entropically disfavored, because of the chain movements required, and enthalpically disfavored, because of the disruption of the enthalpically favored helical state. The fact that association does occur for **3** indicates that a mechanism which involves a dynamic receptor, such as pathway (2) in Figure 1 a, is a viable process for foldamers **1**. The different kinetic behavior exhibited by the two ligands suggests that **1** and **2** associate by a mechanism more like pathway (1) in Figure 1 a, but a pathway that involves significant chain reorganization (pathway (2)) cannot be ruled out.

In conclusion, we have demonstrated that the addition of capping groups to rodlike ligand **2** to yield the dumbbell-shaped ligand **3** does not block its binding to foldamers **1** and has large, length-specific association energies. This result allows the mechanistic conclusions that a dynamic pathway is accessible for the inclusion of hydrophobic molecules in the helical cavity of **1**, and that the molecular recognition by helical foldamers involves at least some deformation of the fully folded helix. It remains to be shown if reorganization of the helix is required or indeed kinetically competitive for systems in which pathway (1) is allowed. Furthermore, the higher affinity and oligomer length specificity of **3** relative to **2** may allow its use as a template for size-selective dynamic syntheses<sup>[17]</sup> of foldamers structurally similar to **1**.

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- [15] We also observed that the saturation molar CD intensity with **3**,  $\Delta\epsilon_\infty$ , also reached a maximum when the length of the oligomer reached the icosamer. This value was twice that observed for rodlike ligand **2** with the icosamer.
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# Tuning the Electrical Conductivity and Self-Assembly of Regioregular Polythiophene by Block Copolymerization: Nanowire Morphologies in New Di- and Triblock Copolymers\*\*

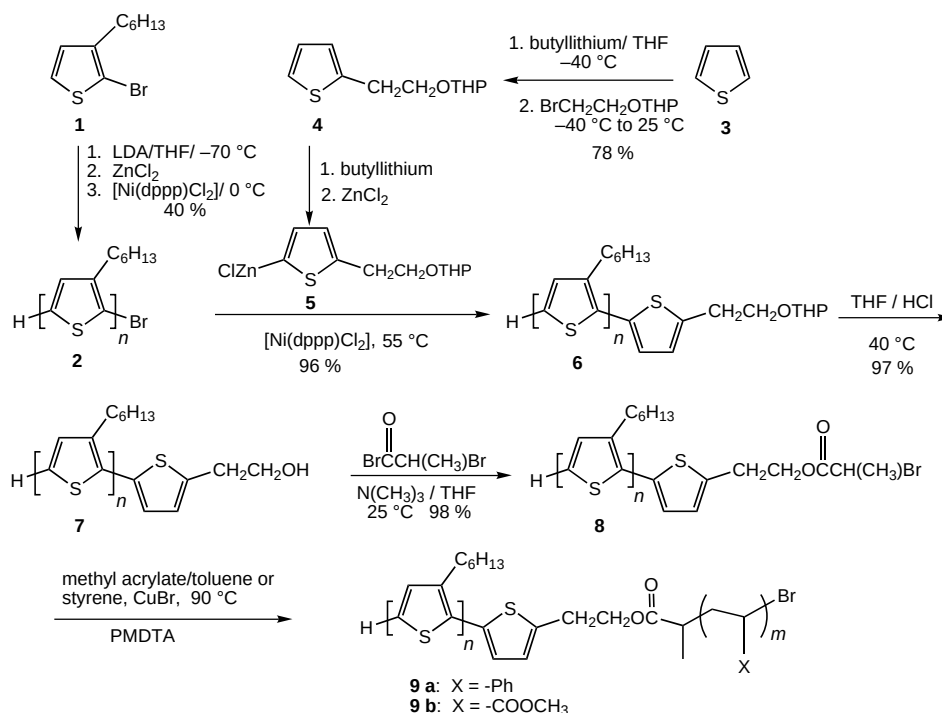
Jinsong Liu, Elena Sheina, Tomasz Kowalewski, and Richard D. McCullough\*

Over two decades ago the discovery of electrical conductivity in conjugated polymers spurred a tremendous amount of effort aimed at the development of practical conducting plastics.<sup>[1]</sup> One of the primary motivations was the hope of fabricating inexpensive, lightweight conducting materials. Those efforts have been coming to fruition in recent years with the development of polymer-based light-emitting diodes,<sup>[2]</sup> field-effect transistors,<sup>[3]</sup> elements for active matrix displays,<sup>[4]</sup> and all-polymer integrated circuits.<sup>[5]</sup> The synthesis and study of regioregular polythiophenes has produced conjugated polymers that self-assemble into well-defined superstructures and has furthered the use of these materials in the aforementioned applications.<sup>[6]</sup> Formation of ordered supermolecular structures in these regioregular materials correlates strongly with their excellent electrical conductivities (thousands or hundreds of  $\text{Scm}^{-1}$  in comparison with a few  $\text{Scm}^{-1}$  for regiorandom polymers). Nevertheless, regioregular polythiophenes still have poor mechanical and processing properties relative to typical flexible polymers.

One approach to solving this problem is to synthesize block copolymers that contain conducting polymer or oligomer units.<sup>[7]</sup> Such a block copolymer<sup>[8]</sup> could self-assemble into a number of nanoscale morphologies, such as lamellar, spherical, cylindrical, and vesicular structures, which would lead to the possibility that new electronic/structural copolymers could be designed, synthesized, and assembled as components in new nano-

devices. Here we present a very easy synthetic method to produce a large number of well-defined block copolymers and polyurethane elastomers containing regioregular polythiophenes. Despite having low percentages of regioregular polythiophenes, these new copolymers have very high conductivities (of the order of a few  $\text{Scm}^{-1}$ ) and form very well defined nanowires that reach lengths in the micron range. In addition, we have found that simply changing the solvent or evaporation conditions allows us to control the nanowire formation and the electrical conductivity of the block copolymer.

The synthesis of diblock copolymers of head-to-tail-coupled poly(3-alkylthiophenes) (HT-PATs) can be accomplished by first preparing a well-defined PAT (polydispersity index (PDI) = 1.2) with 95 % of its end groups<sup>[9]</sup> containing one proton and one bromine atom (**2**; Scheme 1). The method<sup>[10]</sup>



Scheme 1. Synthesis of diblock polymers. LDA = lithium diisopropylamine, dppp = propane-1,3-diylbis(diphenylphosphane), THP = tetrahydropyran.

shown in Scheme 1 is an important modification of methods previously published by our group.<sup>[6, 11]</sup> The reaction was optimized and the polymer end groups were characterized by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS).

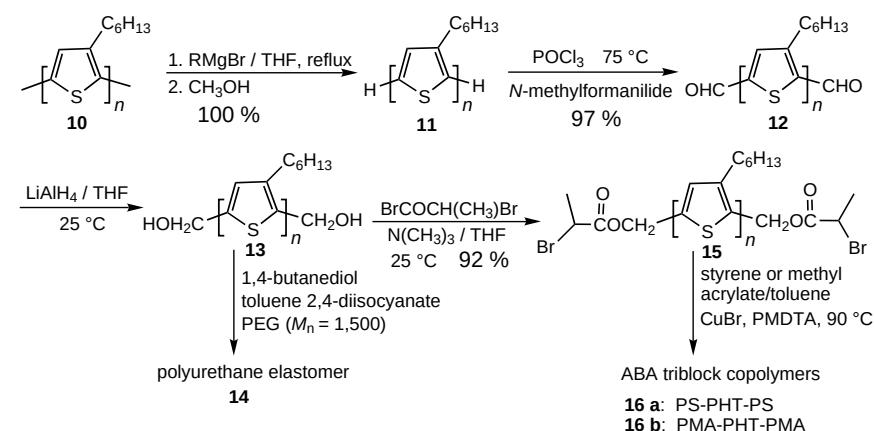
Since PATs are chemically stable polymers, the ability to modify the end groups on one side of the polymer is similar to polymer- or bead-supported organic synthesis. Excess of reagents were used to drive the modification reactions to completion to give > 95 % yield for all of the steps subsequent to the synthesis of the HT-PHT. The purification of the products from all the reaction steps was achieved by simple precipitation and filtration, thus each step of the end-group modification is high yielding (> 95 %) and is facile to accomplish. The HT-PHT **2** is functionalized by reaction with

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thiophene derivative **5** and [Ni(dppp)Cl<sub>2</sub>] (dppp = propane-1,3-diylbis(diphenylphosphane)) to yield polymer **6**.<sup>[12]</sup> De-protection of **6** leads to HT-PHT with one hydroxyl end group (**7**),<sup>[12]</sup> as verified by NMR and MALDI-MS analysis. The hydroxy-terminated PHT (**7**) was further modified by reaction with 2-bromopropionyl bromide to generate an atom transfer radical polymerization (ATRP)<sup>[13]</sup> macroinitiator (**8**).<sup>[14]</sup> Diblock copolymers (for example, **9**) containing PHT can be prepared by the ATRP “living” free-radical polymerization method developed by Matyjaszewski and co-workers to produce a wide variety of conventional polymers. As an example, we have made polyhexylthiophene–polystyrene (PHT-PS; **9a**) and polyhexylthiophene–polymethylacrylate (PHT-PMA; **9b**) by ATRP using **8** as the initiator, styrene or methyl acrylate as the monomer, and CuBr/*N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA) as the catalyst<sup>[15]</sup> (Scheme 1). The percentage of the PS or PMA block is completely controlled by the feed ratio of the monomers, as confirmed by NMR spectroscopy and size-exclusion chromatography.<sup>[16]</sup> High molecular weights and low polydispersities are produced by the combination of using the HT-PHT macroinitiator (**8**) with a low PDI and the “living” nature of the ATRP method.

In addition, regioregular HT-PHT can be functionalized on both the  $\alpha$  and  $\omega$  ends, which allows for the synthesis of PS and PMA triblock copolymers and polyurethane elastomers containing HT-PHT (Scheme 2). Regioregular PHT **10** with a mixture of end groups<sup>[6, 11]</sup> is debrominated by a Grignard metathesis reaction and quenched with water to yield **11**.<sup>[9]</sup> A Vilsmeier reaction on **11** gives polymer **12** as determined by MALDI-MS. The aldehyde end groups on **12** are reduced with LiAlH<sub>4</sub> to yield a PHT terminated by hydroxymethyl groups (**13**). Analysis of the product by MALDI-MS unambiguously proves the incorporation of the hydroxymethyl group to both ends of the polymer chains. We have prepared well-defined triblock copolymers PS-PHT-PS (**16a**) and PMA-PHT-PMA (**16b**) of high molecular weight with low polydispersities from the common polymer (**15**)<sup>[15]</sup> by using ATRP with styrene or methyl acrylate as the monomer.<sup>[16]</sup> Again the percentages of PS or PMA corresponded to the feed ratio of the monomer. In addition, polymer **13** is easily converted<sup>[17]</sup> into polyurethane elastomers (**14**).



Scheme 2. Synthesis of triblock polymers and polyurethane elastomers. PEG = polyethyleneglycol, PMDTA = *N,N,N',N',N''*-pentamethyldiethylenetriamine.

Thin films of all the polymers (PHT-PS (**9a**), PHT-PA (**9b**), polyurethane elastomers (**14**), PS-PHT-PS (**16a**), and PA-PHT-PA (**16b**)) were generated by the slow evaporation of toluene solutions to give magenta to purple films with excellent mechanical properties. These films were oxidized by exposure to I<sub>2</sub> vapor to give multifunctional polymers with high electrical conductivities (Table 1), as determined by four-point probe conductivity measurements. Surprisingly high

Table 1. Conductivity of block copolymers containing HT-PHT.

| PS-PHT diblock copolymers ( <b>9a</b> )       |       |        |       |                        |
|-----------------------------------------------|-------|--------|-------|------------------------|
| wt % of HT-PHT <sup>[a]</sup>                 | 100 % | 37 %   | 22 %  | 14 %                   |
| average M <sub>n</sub> <sup>[b]</sup>         | 16800 | 30200  | 41400 | 53400                  |
| M <sub>w</sub> /M <sub>n</sub> <sup>[b]</sup> | 1.28  | 1.31   | 1.32  | 1.45                   |
| conductivity [S cm <sup>-1</sup> ]            | 110   | 4.7    | 0.08  | 0.14                   |
| PS-PHT-PS triblock copolymers ( <b>16a</b> )  |       |        |       |                        |
| wt % of HT-PHT <sup>[a]</sup>                 | 100 % | 52 %   | 26 %  | 7.7 %                  |
| average M <sub>n</sub> <sup>[b]</sup>         | 17900 | 25500  | 38100 | 93600                  |
| M <sub>w</sub> /M <sub>n</sub> <sup>[b]</sup> | 1.23  | 1.21   | 1.25  | 1.51                   |
| conductivity [S cm <sup>-1</sup> ]            | 96    | 5.3    | 0.43  | 0.05                   |
| PA-PHT-PA triblock copolymers ( <b>16b</b> )  |       |        |       |                        |
| wt % of HT-PHT <sup>[a]</sup>                 | 100 % | 45 %   | 18 %  | 10 %                   |
| average M <sub>n</sub> <sup>[b]</sup>         | 17900 | 29700  | 50400 | 72300                  |
| M <sub>w</sub> /M <sub>n</sub> <sup>[b]</sup> | 1.23  | 1.29   | 1.41  | 1.66                   |
| conductivity [S cm <sup>-1</sup> ]            | 96    | 3.3    | 1.6   | 0.076                  |
| Polyurethane ( <b>14</b> )                    |       |        |       |                        |
| wt % of HT-PHT                                | 10 %  | 6.40 % |       | 0.60 %                 |
| conductivity [S cm <sup>-1</sup> ]            | 0.13  | 0.048  |       | 4.6 × 10 <sup>-5</sup> |

[a] Determined by <sup>1</sup>H NMR spectroscopy. [b] Determined by GPC with polystyrene as standard.

electrical conductivities were found in all of the copolymer samples. While many copolymers containing conjugated polymers and other polymers and blends have been prepared, no one has reported conductivity values near to those reported here (Table 1). While 100% HT-PHT has a conductivity of 110 S cm<sup>-1</sup>, a block copolymer of PHT-PS (**9a**) containing 37% HT-PHT has a conductivity of about 5 S cm<sup>-1</sup>. The conductivity drops down to 0.1 S cm<sup>-1</sup> for samples containing approximately 22% of HT-PHT or less. The conductivity of the block copolymers largely depends on the ratio of the conducting and nonconducting blocks and is related to the structural assembly. The PS-PHT-PS triblock copolymers (**16a**) have conductivities as high as 5 S cm<sup>-1</sup> for a sample with 52% PHT. Our conducting polyurethane copolymers (**14**) exhibit conductivities as high as 10<sup>-1</sup> S cm<sup>-1</sup>, which is much higher than other polyurethane conjugative copolymers or blends reported in the literature (10<sup>-4</sup> S cm<sup>-1</sup>).<sup>[18]</sup> Conductivities for blends of conjugative polymers with polyvinyl chloride and other conventional polymers have also been found to exhibit low conductivities (in the 10<sup>-4</sup> S cm<sup>-1</sup> range).<sup>[18]</sup> All of our block copolymers also have excellent film-forming and good mechanical properties including elasticity in the polyurethane samples.

We have found that thin and ultrathin films these block copolymers containing

polythiophene that were prepared by casting from toluene followed by free evaporation of a solvent reproducibly self-assembled into very well-defined “nanowires” spaced laterally by 30–40 nm (which corresponds to a fully extended HT-PHT block) with lengths on the order of micrometers (Figure 1). Lower percentages of PHT also lead to similar morphologies as found in drop-cast films, however, a clear dilution factor of the PHT is observed. As an example, an atomic force micrograph (AFM) micrograph of a PS-PHT (**9a**) sample is shown (Figure 2), where the weight percentage of PHT is 37 % and the film was cast from a 0.5 mg mL<sup>-1</sup> solution in toluene. The samples were then imaged using the variable-tapping force technique (developed in recent years) with the purpose of using tapping-mode AFM to study mechanical properties of materials at the nanoscale.<sup>[19]</sup> Interestingly, “nanowires” were clearly discernible only under “hard tapping” conditions (tens to hundreds nanonewtons) and were barely identifiable when imaged with forces of the order of just a few nanonewtons. The formation of a “nanowire” structure is undoubtedly dictated by the immiscibility of polystyrene and poly(3-hexylthiophene). Under such circumstances nanowires can be predicted to have a core–shell architecture, with the minority component (polythiophene) constituting the core. Such a sheathed structure is indeed consistent with our variable-force experiments. Under “light tapping” conditions, the tip–sample force is not high enough to penetrate through the outer sheath of the nanowires. Since the polystyrene segments in the sheath can mix with the chains from adjacent aggregates, the boundaries between nanowires are not well resolved. In contrast, under “hard tapping” conditions the probe–sample force is high enough to deform the outer sheath and “sense” the presence of a rigid core. These structures have also been observed in transmission electron microscopy (TEM) experiments as well.

The strong tendency of regioregular poly(alkylthiophenes) to self-assemble into stacked aggregates raises a question about the role of this intrinsic self-assembly in the formation of nanowires. An important observation in this regard is

that thin and ultrathin films prepared by spin-coating from chloroform had distinctly different, “uninteresting”, morphology without any indications of long-range order (Figure 3). Suppression of the formation of nanowires under these conditions may be pointing to the key role of the intrinsic self-assembly of polythiophene: this process might have been kinetically suppressed here because of the high rate of solidification associated with spin-coating from a highly volatile solvent. This kinetic argument was further supported by experiments in which thin films were again cast from

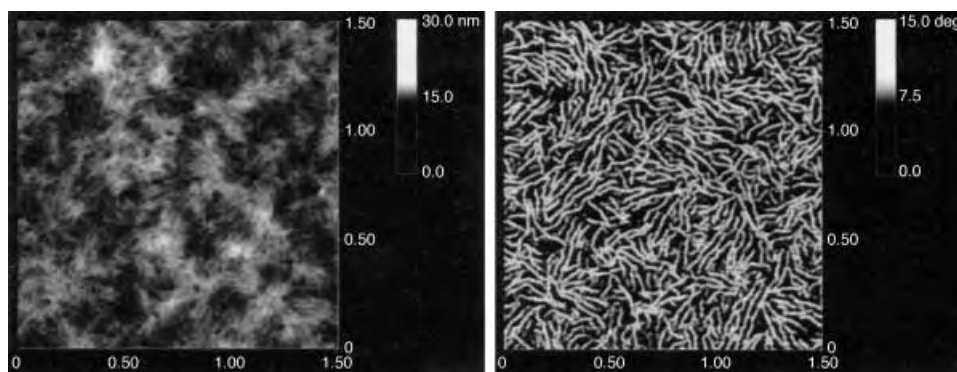


Figure 1. “Nanowire” morphology in poly(3-hexylthiophene)-b-poly(styrene) copolymers solvent-cast from toluene and visualized with tapping-mode AFM. Left: height; right: phase (see text). These and subsequent images use gray-scale coding, with darker tones corresponding to lower values (for example, lower heights.)

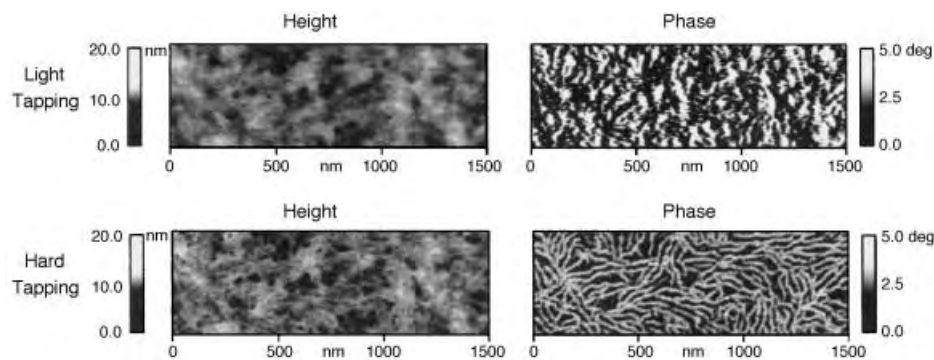


Figure 2. Under “light tapping” conditions (top) only the outer, partially overlapping shells of aggregates are visualized and the nanowire morphology is not apparent. In contrast, under “hard tapping” conditions (bottom), the probe interacts with the outer shells with sufficient force to “sense” the presence of rigid poly(3-alkylthiophene) cores.

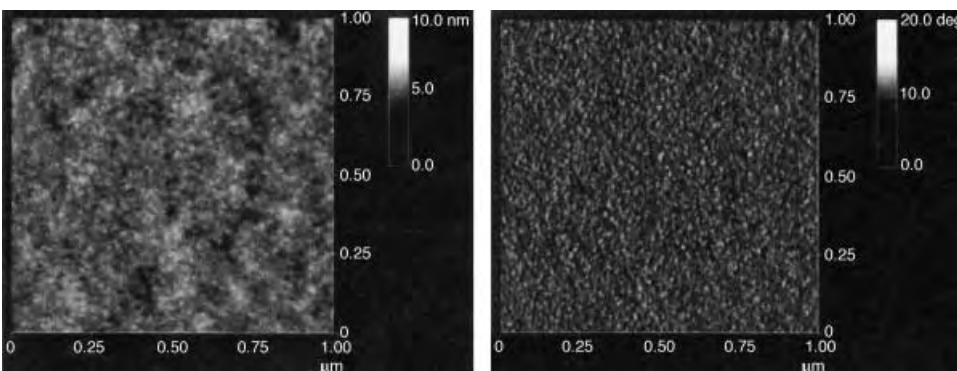


Figure 3. Tapping-mode AFM images of ultrathin films of poly(3-hexylthiophene)-b-poly(styrene) spin-coated from chloroform. Left: height; right: phase.



toluene, but under a stream of nitrogen. Under these accelerated evaporation conditions the formation of nanowires was also totally suppressed.

The nanowire morphologies found in block copolymers<sup>[20]</sup> of regioregular poly(alkylthiophenes) points to the possibility of guiding the intrinsic self-assembly of sufficiently regular conjugated polymer chains by coupling them chemically to incompatible segments. In the simplest case, the obtained structure is the result of interplay between different driving forces of self-assembly ( $\pi$  stacking versus phase separation). To rephrase this point, the free-energy landscape of rigid conjugated molecules has few deep local minima as a result of strong  $\pi$  interactions which cannot be easily explored under normal conditions. Thus, the molecules are easily trapped in the states with a high degree of local stacking, but at the same time there is a high concentration of defects that adversely affects the bulk properties. Copolymerization with incompatible flexible segments brings into play competing driving forces of self-assembly that result in "more interesting" and easier to explore free-energy landscapes. Identifying the overall features of those energy landscapes may give us the ability to exercise control of the resulting nanostructures, and effectively pave the way to applications of conjugated polymers as building blocks for future nanoscale and molecular level electronic devices.

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- [11] Polymer **2** was prepared by the following method: Distilled diisopropylamine (1.4 mL, 10 mmol) and 2.58 M *n*BuLi (3.7 mL, 9.5 mmol) were dissolved in dry THF (50 mL) at  $-78^{\circ}\text{C}$ . The mixture was then warmed to room temperature over 5 min and then cooled to  $-78^{\circ}\text{C}$ . The monomer 2-bromo-3-hexylthiophene (2.5 g, 10 mmol) was added to the freshly generated lithium diisopropylamine and the reaction stirred at  $-70^{\circ}\text{C}$  for 1 h. Anhydrous  $\text{ZnCl}_2$  (1.43 g, 10.5 mmol) was then added at  $-70^{\circ}\text{C}$  and the reaction was stirred for 1 h. The reaction was warmed to  $0^{\circ}\text{C}$  and  $[\text{Ni}(\text{dppp})\text{Cl}_2]$  (35 mg, 0.065 mmol, 0.6 mol %) was added. The mixture was warmed to room temperature and then stirred for an additional 30 min. Polymer **2** was precipitated with methanol. The polymer was washed/fractionated by Soxhlet extraction with methanol, hexane, dichloromethane, and tetrahydrofuran. The THF fraction was characterized and used in further experiments.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 6.98 (s, 1H), 2.79 (t,  $J$  = 7.7 Hz, 2H), 1.62 (m, 2H), 1.48 (m, 2H), 1.36 (m, 4H), 0.90 (t,  $J$  = 6.3 Hz, 3H); MALDI-MS:  $M_n$  = 7634 (PDI = 1.14, end groups: H/Br ca. 95 %, H/H ca. 4 %, Br/Br ca. 1 %), 7729.02 [ $M^+$ ] (calcd: 7730.12, given a degree of polymerization of 46 for the PHT); GPC:  $M_n$  = 16,800 (PDI = 1.28).
- [12] Characterization of **6**:  $^1\text{H}$  NMR 6.98 (s, 49H), 6.89 (d,  $J$  = 3.3 Hz, 1H), 6.80 (d,  $J$  = 3.3 Hz, 1H), 4.65 (t,  $J$  = 3.7 Hz, 1H), 3.82 (m, 2H), 3.65 (m, 2H), 3.11 (t,  $J$  = 6.6 Hz, 2H), 2.79 (t,  $J$  = 7.63 Hz, 100H), 1.62 (m, 98H), 1.48–1.36 (m, 300H), 0.9 (t,  $J$  = 6.3 Hz, 150H); MALDI-MS:  $m/z$ : 7859.36 [ $M^+$ ] (calcd: 7860.88, given a degree of polymerization of 46); GPC:  $M_n$  = 17000 (PDI = 1.28). Characterization of **7**:  $^1\text{H}$  NMR  $\delta$  = 6.98 (s, 49H), 3.89 (t,  $J$  = 6.6 Hz, 2H), 3.07 (t,  $J$  = 6.6 Hz, 2H), 2.79 (t,  $J$  = 7.6 Hz, 99H), 1.62 (m, 99H), 1.48–1.36 (m, 300H), 0.9 (t,  $J$  = 6.3 Hz, 148H); MALDI-MS:  $m/z$ : 7776.88 [ $M^+$ ] (calcd: 7777.35, given a degree of polymerization of 46); GPC:  $M_n$  = 16740 (PDI = 1.28).
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- [14] Characterization of **8**:  $^1\text{H}$  NMR 6.98 (s, 49H), 4.38 (m, 1H), 4.40 (m, 2H), 3.19 (t,  $J$  = 6.6 Hz, 2H), 2.79 (t,  $J$  = 7.6 Hz, 99H), 1.83 (d,  $J$  = 6.6 Hz, 3H), 1.62 (m, 99H), 1.48–1.36 (m, 300H), 0.9 (t,  $J$  = 6.3 Hz, 148H).
- [15] Typical ATRP: PHT macroinitiator (**8** or **15**; 0.1 g, ca. 0.012 mmol) was dissolved in the mixture of freshly distilled toluene and monomers (1:1 when monomer is styrene, 3:1 when monomer is methyl acrylate). CuBr (0.018 g, 0.125 mmol) and PMDTA (0.027 g, 0.125 mmol) were added to this solution. After being purged with nitrogen for 15 mins, the solution was placed into an oil bath at  $90^{\circ}\text{C}$ . Copolymers with different ratios of PHT were obtained by pouring the solution into methanol after different periods of time. After precipitation and filtration, the polymer was dissolved in THF and passed through an  $\text{Al}_2\text{O}_3$  column to eliminate the catalyst.
- [16] See Supporting Information.
- [17] Polyurethane elastomers were prepared by either one-shot process or two-shot process. See Supporting Information.
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# From Surfactant–Inorganic Mesostructures to Tungsten Nanowires\*\*

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Surfactant–inorganic mesostructured composite materials<sup>[1–3]</sup> have attracted great interest over the past decade due to their potential applications as catalysts, separation membranes, chemical sensors, and in solid-electrolyte and optoelectronic devices.<sup>[3–8]</sup> However, to obtain these highly ordered mesoporous materials, removal of the surfactant species from the mesostructured composites is critical. Here we report on a simple and versatile vacuum-controlled pyrolysis procedure for the removal of the surfactant species from lamellar mesostructured composites of tungsten oxide with cetyltrimethylammonium surfactant cations (WO-L). In this process, pyrolysis and carbothermal reaction of WO-L take place in vacuo at 500–850 °C, and bulk quantities of uniform metallic tungsten nanowires with diameters of 20–80 nm and lengths ranging from 5 to 30  $\mu\text{m}$  are obtained. We believe that raising the processing temperature induces curvature in the lamellar structure of the thermally unstable inorganic–surfactant precursor and finally leads to the formation of tubular structures. The inorganic–surfactant precursor may act as a template, which confines the carbothermal reaction and results in tungsten nanowires. This may represent a universal approach for the synthesis of nanowires of other transition metals, such as Co, Ni, and Cu, by vacuum pyrolysis/carbothermal (VPC) treatment of lamellar inorganic–surfactant precursors.

The discovery of carbon nanotubes<sup>[9]</sup> raised the question whether compounds with layered structures analogous to that of graphite can form nanotubes or one-dimensional nanowires. It was partially answered by the synthesis of  $\text{WS}_2$ ,  $\text{MoS}_2$ ,<sup>[10]</sup> and  $\text{NiCl}_2$ <sup>[11]</sup> nanotubes. We speculated that lamellar composites consisting, for example, of tungsten oxide or the oxide or sulfide of Ni, Co, or Cu and surfactants could serve as precursors for metallic nanowires or nanotubes by reduction.

Mesolamellar WO-L was prepared by the reaction of sodium tungstate ( $\text{Na}_2\text{WO}_4$ ) and cetyltrimethylammonium bromide (CTAB) under mild hydrothermal conditions<sup>[12, 13]</sup> in

85–90 % yield. Elemental analysis and thermogravimetric/differential thermal analysis results showed a molar ratio of surfactant to tungsten of about 2:1. The lamellar nature of WO-L was confirmed by the low-angle X-ray powder-diffraction (XRD) pattern (Figure 1 a).

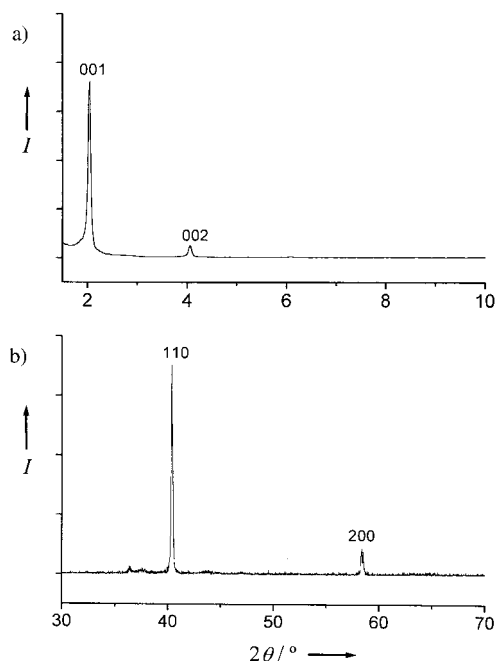


Figure 1. a) Low-angle XRD pattern of WO-L prepared under mild hydrothermal conditions. b) XRD pattern of the VPC product indicating the presence of bcc W.

The VPC treatment of WO-L was carried out in a conventional tube furnace (Figure 2). Control of the temperature gradient and gas pressure during the VPC reaction was a key factor, otherwise the precursors cracked into platelets or particles. The final black products were characterized on a Bruker D8-advance X-ray diffractometer with  $\text{Cu}_{K\alpha}$  radiation ( $\lambda = 1.54178 \text{ \AA}$ ). In the XRD pattern of the final product (Figure 1 b), reflections could be readily indexed to the bcc phase of W with a lattice constant of  $a = 3.165 \text{ \AA}$ .

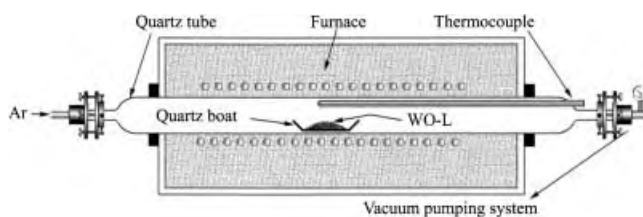


Figure 2. Schematic representation of the tube furnace used for VPC treatment of WO-L.

Transmission electron microscopy (TEM) images were taken with a Hitachi H-800 transmission electron microscope operated at 200 kV. The TEM image of a typical product (Figure 3 a) showed primarily wirelike structures with diameters of 20–80 nm and lengths ranging from several micrometers to 30  $\mu\text{m}$ . In addition to the nanowires, platelets and particles were obtained. Analysis by electron-induced X-ray

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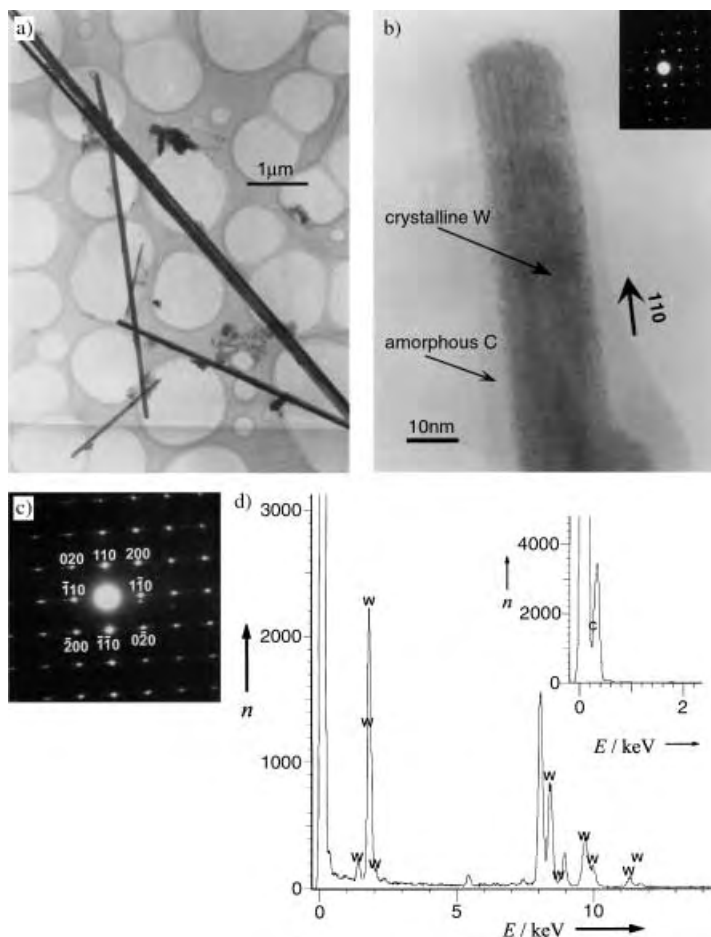


Figure 3. a) TEM image showing the morphology of the W nanowires obtained by the VPC method. b) HRTEM image of an individual W nanowire. The SAED pattern (inset) reveals the  $[110]$  growth direction of the bcc W nanowire. c) Diffraction indexes of the SAED pattern in (b). d) Compositions of the core and sheath (inset) parts of the W nanowire shown in (b), obtained by EDX analysis.

fluorescence (EDX) showed that the platelets were composed of tungsten, and the particles were usually composed of tungsten or amorphous carbon. The average yield of the nanowires, estimated from TEM images of samples from different syntheses, was about 20%. The coexistence of platelike and granular W products in the samples, as well as the relatively large mean diameters (about 50 nm, based on TEM images) of the W nanowires, might explain why inhomogeneous peak broadening was not observed in the XRD patterns. The reproducibility of the synthesis was satisfactory. Under optimal experimental conditions, the yield of tungsten nanowires was never less than 10%. The mean dimensions and size distributions of nanowires obtained in different synthetic batches under the same reaction conditions (hydrothermal precursor synthesis and VPC) were about the same.

High-resolution transmission electron microscopy (HRTEM) images of W nanowires were taken on a JEOL-2010 transmission electron microscope. The HRTEM image of an individual nanowire (Figure 3b) provided further insight into the structure of these products. The selected-area electron diffraction (SAED) pattern recorded perpendicular

to the growth axis of the single nanowire (Figure 3c) could be attributed to the  $[001]$  zone axis diffraction of bcc W, and this suggested that the nanowire grew along the  $[110]$  direction. This conclusion was also confirmed by the  $[110]$  lattice fringes perpendicular to the nanowire axis, with a spacing of 2.24 Å. We also employed SAED to characterize the nanowires obtained in different syntheses, as well as different parts of the same nanowire. All electron diffraction patterns indicated exclusively the same  $[110]$  orientation of the nanowire, and this implies that these W nanowires are single crystallites rather than multidomain polycrystallites (random orientations would usually be expected in different parts of a multidomain nanowire).

An additional important detail was found in the HRTEM image: a clear amorphous coating sheath on the nanowire core. The EDX analysis of these individual nanowires showed that they contained only W and a trace of C (Figure 3d). The amorphous outer sheath was composed only of C (inset of Figure 3d). We attribute the amorphous C coatings on the W nanowires to residues of the vacuum-pyrolysis carbothermal treatment of the inorganic–surfactant precursor.

How are atoms or other building blocks assembled into such structures with nanoscale diameters but long lengths, and how can we understand the mechanism by which the nanowires are formed in this novel VPC approach? On the basis of the needle morphology, we propose a new growth model for these W nanowires (Figure 4). The nanowire formation can be

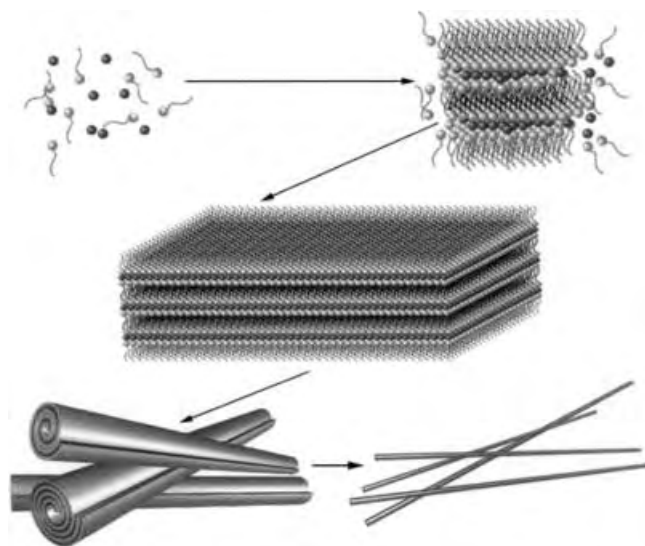


Figure 4. Schematic depiction of different periods in a typical VPC process. The dark balls represent inorganic components such as  $\text{WO}_4^{2-}$ , and the light balls correspond to the head groups of the  $\text{CTA}^+$  cations.

divided into four steps. 1) The  $\text{CTA}^+$  cations condense into aggregates in which the tungstate anions are intercalated in the interspaces between the head groups of  $\text{CTA}^+$  to form  $\text{CTA}-\text{WO}_4$  ion pairs. 2) The continuing condensation process generates more highly ordered lamellar assemblies. These mesolamellar structures were confirmed by low-angle X-ray diffraction (see Figure 1a). 3) When heated in vacuo with gradually increasing temperature, these lamellar sheets begin to roll onto themselves and finally form separate scrolls

consisting of CTA<sup>+</sup> cations and tungstate anions. 4) With increasing furnace temperature, tungstate is reduced by pyrolytic carbon derived from CAT<sup>+</sup> to give W metal with a shape defined by the scrolls, which could serve as micro-reactors for the VPC process and thus are responsible for the ultimate wirelike shape of W. The VPC process should involve a tubular intermediate that results from confinement of the scrolls. However, with the removal of surfactant molecules and crystallization of tungsten metal, these tubular nanostructures would finally transform into the nanowire products.

To substantiate our hypothesis, we performed control experiments. The tungstate and surfactants were mixed mechanically, but no lamellar composite structures were present in these mixtures according to low-angle XRD data. The same VPC operations were performed on these mixtures. However, only W particles were observed. In addition, we performed a more stringent test of our model by preparing Ni, Co, Cu, and Cd nanowires (see Supporting Information). The fundamental experimental results were in good agreement with our suggested VPC model (see Supporting Information). The above studies illustrate that the controlled VPC treatment of inorganic–surfactant lamellar precursors might be a general approach for the synthesis of crystalline nanowires or nanotubes.

### Experimental Section

Analytical-grade Na<sub>2</sub>WO<sub>4</sub> (3 mmol) and CTAB (9 mmol) were dissolved in distilled water to form a homogeneous solution. The pH of the solution was adjusted to the range of 8–10 by addition of aqueous NH<sub>3</sub> or HCl. The mixture was stirred vigorously for 1 h and then sealed in a Teflon-lined stainless steel autoclave and kept at 140 °C for 6 d. The solid WO-L product was collected by filtration, washed with distilled water and absolute ethanol, and then dried in vacuo at 80 °C for 12 h. The calculated yield was about 85–90 % on the basis of W.

The VPC treatment was carried out in a conventional tube furnace (see Figure 2). The as-prepared WO-L (400 mg) was placed in a quartz boat. The quartz boat was placed in the hot zone inside the quartz tube and the content calcined and pyrolyzed for 10 h at 100 to 850 °C in a high-purity argon atmosphere (99.999 %) with a pressure range of 10<sup>−2</sup>–10<sup>−3</sup> atm. The furnace temperature was first increased to 400 °C over 4 h and then held at that temperature for 2 h to ensure completion of the rolling process of the lamellar precursor. Then the temperature was raised to 850 °C over 2 h and kept at that temperature for 2 h. Finally, the temperature was allowed to descend to room temperature. In the whole process, the reaction temperature was controlled exactly at ± 1 K by a built-in temperature-control unit in the tube furnace.

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## Dynamic Kinetic Resolution and Desymmetrization of Enantiotopic Groups by Cyclodehydration of Racemic or Prochiral $\delta$ -Oxoesters with (*R*)-Phenylglycinol: Enantioselective Synthesis of Piperidines\*

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The development of efficient methods to produce an optically pure enantiomer is of fundamental importance, particularly for the synthesis of bioactive natural or synthetic products. Today, enzyme-mediated desymmetrizations of either prochiral or *meso* substrates, generally diesters, and enzyme-catalyzed kinetic resolutions of racemates constitute classical approaches for the synthesis of enantiopure compounds, and have become powerful synthetic tools.<sup>[1]</sup> In contrast, in spite of the impressive advances in the field of chemical, nonenzymatic, enantioselective desymmetrizations over the last few years, the chemical differentiation of two enantiotopic functional groups has been little developed.<sup>[2]</sup> On the other hand, the major drawback of kinetic resolution, like conventional resolution processes, is that the maximum yield of one enantiomer is always limited to 50 %. However, this situation dramatically changes when racemic substrates have a chirally labile stereogenic center that is capable of undergoing racemization *in situ* during the reaction (dynamic kinetic resolution (DKR)).<sup>[3]</sup>

In the context of our studies on the synthesis of enantiopure piperidine derivatives from chiral nonracemic bicyclic lactams formed by cyclodehydration of  $\delta$ -oxoesters and (*R*)- or (*S*)-

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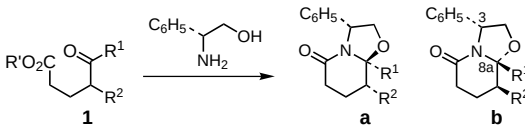
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phenylglycinol,<sup>[4]</sup> we report herein the preparation of poly-substituted lactams by DKR of racemic  $\delta$ -oxoacid derivatives, enantioselective desymmetrization of prochiral  $\delta$ -oxodiester, and tandem DKR–diastereotopic differentiation of racemic  $\delta$ -oxodiester, which ultimately leads to diversely substituted enantiopure piperidines.

Cyclodehydrations<sup>[5]</sup> with a variety of racemic aldehyde esters and ketoacids that bear a substituent (alkyl or aryl) at the epimerizable carbon atom  $\alpha$  to the aldehyde (**1a–c**) or ketone (**1d–f**)<sup>[6]</sup> group (Table 1) stereoselectively afforded a lactam as the major product, accompanied by minor amounts of a second stereoisomer ( $\approx 4:1$ ),<sup>[7]</sup> which clearly indicates that DKR had occurred.<sup>[8]</sup>

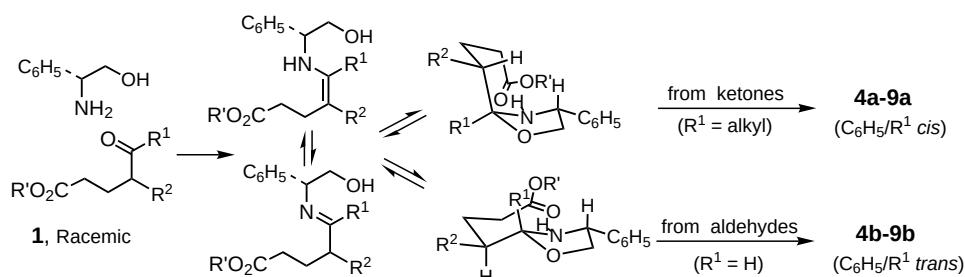
Table 1. DKR by cyclodehydration of racemic  $\delta$ -oxoacid derivatives with (*R*)-phenylglycinol.



| Entry | Substrate                | R' | R <sup>1</sup> | R <sup>2</sup>                                                                                  | t [h] | Lactam   | a/b                    | Yield [%] |
|-------|--------------------------|----|----------------|-------------------------------------------------------------------------------------------------|-------|----------|------------------------|-----------|
| 1     | <b>1a</b>                | Me | H              | Et                                                                                              | 18    | <b>4</b> | 20:80 <sup>[b]</sup>   | 80        |
| 2     | <b>1b</b>                | Me | H              | CH <sub>2</sub> CH <sub>2</sub> C(S <sub>2</sub> C <sub>3</sub> H <sub>6</sub> )CH <sub>3</sub> | 14    | <b>5</b> | 17:83 <sup>[c]</sup>   | 70        |
| 3     | <b>1c</b>                | Me | H              | C <sub>6</sub> H <sub>5</sub>                                                                   | 24    | <b>6</b> | 16:84 <sup>[b]</sup>   | 58        |
| 4     | <b>1d</b>                | H  | Me             | Et                                                                                              | 24    | <b>7</b> | 78:22 <sup>[c]</sup>   | 60        |
| 5     | <b>1e</b> <sup>[a]</sup> | Me | Me             | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>                                                      | 14    | <b>8</b> | 80:20 <sup>[b]</sup>   | 76        |
| 6     | <b>1f</b>                | H  |                | –(CH <sub>2</sub> ) <sub>4</sub> –                                                              | 24    | <b>9</b> | 79:21 <sup>[c,d]</sup> | 70        |

[a] Catalytic amounts of *p*-TsOH were added. [b] Calculated by means of <sup>1</sup>H NMR spectroscopy. [c] Calculated by using HPLC. [d] The configuration of **9a** was confirmed by X-ray crystallographic analysis.

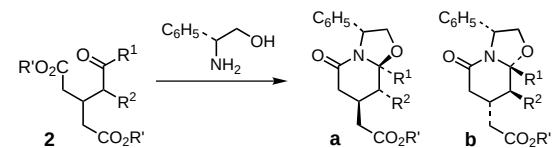
The stereochemical outcome of these reactions<sup>[9]</sup> can be accounted for by considering that the mixture of four diastereomeric oxazolidines formed initially is in equilibrium through the corresponding imines–enamines, and that subsequent lactamization takes place faster through a chairlike transition state in which the substituent R<sup>2</sup> is equatorial, thus leading predominantly to isomers in which R<sup>1</sup> and R<sup>2</sup> are *cis* (Scheme 1). The preferential formation of isomers **b** (C<sub>6</sub>H<sub>5</sub> and R<sup>1</sup> = H are *trans*) from aldehydes **1a–c** (Table 1, entries 1–3) and isomers **a** (C<sub>6</sub>H<sub>5</sub> and R<sup>1</sup> = alkyl are *cis*) from ketones **1d–f** (Table 1, entries 4–6)<sup>[10]</sup> indicates that lactamization occurs faster from the diastereomeric oxazolidine that allows the approach of the carboxylate group to the nitrogen atom by the most accessible face, that is *anti* with respect to C<sub>6</sub>H<sub>5</sub> (from aldehyde esters) or to both C<sub>6</sub>H<sub>5</sub> and R<sup>1</sup> (from ketoacids).



Scheme 1. Imine–enamine equilibrium and subsequent lactamization in the formation of **4–9**.

To study enantioselective desymmetrizations of prochiral  $\delta$ -oxodiester with (*R*)-phenylglycinol, we selected the glutaric and pimelic acid derivatives **2a–b** and **3a**, respectively.<sup>[6]</sup> Interestingly, cyclodehydration<sup>[5]</sup> of aldehyde diester **2a** and ketodiester **2b** with (*R*)-phenylglycinol stereoselectively afforded lactams **10b** and **11a**, respectively, as the major products, together with minor amounts (4:1) of a second diastereomer, **10a** and **11b**, respectively (Table 2, entries 1 and 2). Similarly, cyclodehydration of the prochiral aldehyde **3a** gave lactams **14** in very high stereoselectivity (**14a/14b** 1:9; Table 3, entry 1).<sup>[7]</sup>

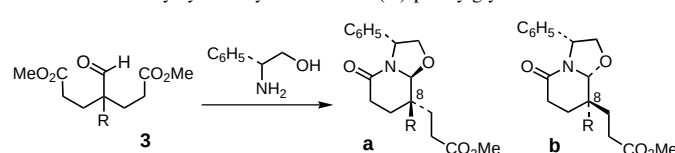
Table 2. Enantioselective desymmetrization of prochiral  $\delta$ -oxodiester and tandem DKR–diastereoselective differentiation of racemic  $\delta$ -oxodiester.



| Entry | Substrate                | R' | R <sup>1</sup> | R <sup>2</sup> | t [h] | Lactam    | a/b                    | Yield [%] |
|-------|--------------------------|----|----------------|----------------|-------|-----------|------------------------|-----------|
| 1     | <b>2a</b>                | Me | H              | H              | 8     | <b>10</b> | 20:80 <sup>[c]</sup>   | 95        |
| 2     | <b>2b</b> <sup>[a]</sup> | Et | Me             | H              | 18    | <b>11</b> | 82:18 <sup>[c,d]</sup> | 77        |
| 3     | <b>2c</b>                | Et | H              | Et             | 14    | <b>12</b> | 20:80 <sup>[e]</sup>   | 77        |
| 4     | <b>2d</b> <sup>[b]</sup> | Et | Me             | <i>n</i> Pr    | 24    | <b>13</b> | 85:15 <sup>[e]</sup>   | 54        |

[a] Catalytic amounts of *p*-TsOH were added. [b] Catalytic amounts of AcOH were added. [c] Calculated by means of HPLC. [d] The configuration of **11a** was confirmed by X-ray crystallographic analysis. [e] Calculated by using <sup>1</sup>H NMR spectroscopy.

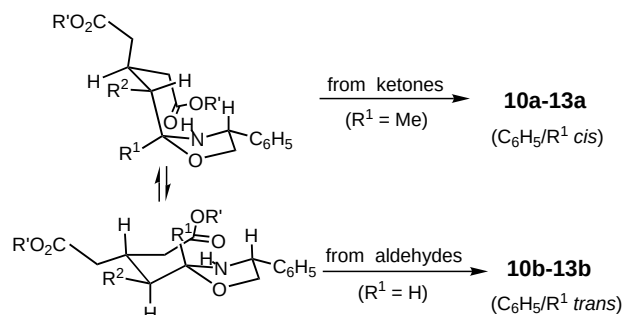
Table 3. Enantioselective desymmetrization of prochiral 4-formylpimelic acid derivatives by cyclodehydration with (*R*)-phenylglycinol.



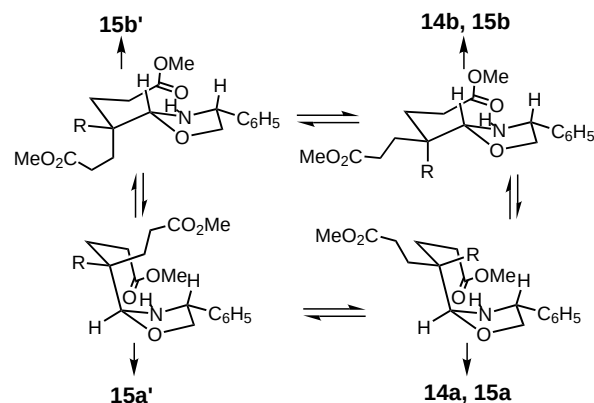
| Entry | Substrate | R  | t [h] | Lactam    | a/b                    | Yield [%] |
|-------|-----------|----|-------|-----------|------------------------|-----------|
| 1     | <b>3a</b> | H  | 20    | <b>14</b> | 10:90 <sup>[a]</sup>   | 67        |
| 2     | <b>3b</b> | Et | 24    | <b>15</b> | 10:90 <sup>[b,c]</sup> | 50        |

[a] Calculated by means of HPLC. [b] Calculated by using <sup>1</sup>H NMR spectroscopy. [c] Isomers **15a** and **15b** were isolated accompanied by their respective C-8 epimers (**15a'** and **15b'**; 1:1 mixtures).

The above results can be rationalized by taking into account that, after the formation of the corresponding oxazolidines, lactamization occurs faster through a chairlike transition state in which the diastereotopic acetate (Scheme 2; from **2a** and **2b**) or propionate (Scheme 3; from **3a**) chain that does not undergo cyclization is equatorial. In accordance with this interpretation, the presence of an ethyl substituent at the prochiral carbon atom in **3b**<sup>[6]</sup> suppresses the discrimination between the two propionate chains (Table 3, entry 2). In this case, either the ethyl



Scheme 2. Lactamization step in the formation of **10–13**.



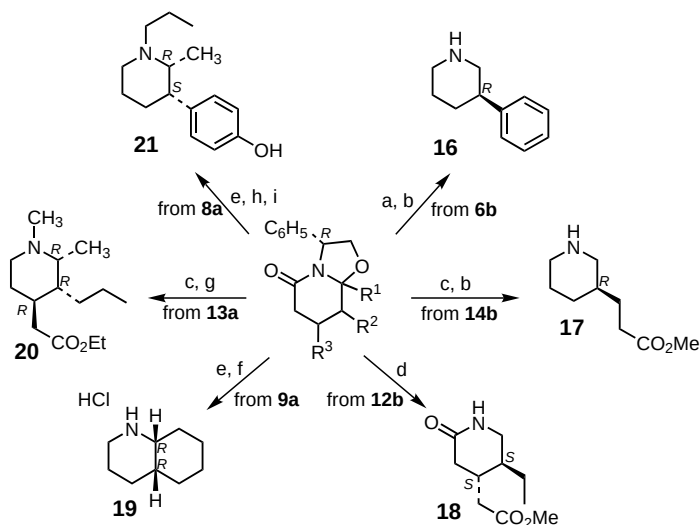
Scheme 3. Lactamization step in the formation of **14** and **15**.

substituent or one of the propionate chains is axially oriented (Scheme 3).

Finally, as could be expected from the above results, treatment of racemic  $\delta$ -oxodiester **2c** or **2d**<sup>[6]</sup> with (*R*)-phenylglycinol under the usual conditions predominantly afforded one of the eight possible stereoisomers, **12b** or **13a**, respectively (Table 2, entries 3 and 4). Three stereogenic centers with a well-defined absolute configuration have been generated in a single synthetic step. Minor amounts of the respective isomers **12a** or **13b** were also isolated.<sup>[7]</sup> These reactions involve DKR, with epimerization of the configurationally labile stereocenter in the substrate, and differentiation of the two diastereotopic acetate chains via a transition state in which the substituents  $R^2$  and  $\text{CH}_2\text{CO}_2\text{Et}$  of the incipient chairlike six-membered lactam are equatorial (Scheme 2,  $R^2 = \text{alkyl}$ ). In all cases, isomers **b** ( $\text{C}_6\text{H}_5$  and  $R^1 = \text{H}$  are *trans*) are the major products in the cyclodehydrations from aldehydes, whereas bicyclic *cis*  $\text{C}_6\text{H}_5/\text{Me}$  lactams **a** are the main products from ketones.

The substituted chiral lactams **4–14** are immediate precursors of a variety of valuable enantiopure piperidine and perhydroquinoline derivatives, including functionalized 3-alkyl-, 3-aryl-, 2,3-dialkyl-, and 2-alkyl-3-arylpiperidines, as well as diversely substituted 4-piperidineacetates. Thus, after removal of the chiral auxiliary, bicyclic lactams **6b**, **14b**, and **12b** were converted into 3-phenylpiperidine **16**, 3-piperidinepropionate **17**, which is an intermediate in the synthesis of anti-obesity drugs,<sup>[11]</sup> and *trans*-3-ethyl-4-piperidineacetate **18**, the enantiomer of a crucial intermediate in the synthesis of benzo[*a*]- and indolo[2,3-*a*]quinolizidine alkaloids<sup>[12]</sup>

(Scheme 4). Similarly, after stereoselective opening of the oxazolidine ring, lactams **9a**, **13a**, and **8a** were converted into *cis*-perhydroquinoline **19**, polysubstituted piperidine **20**, and *cis*-2-alkyl-3-arylpiperidine **21**, an analogue of the antipsychotic drug preclamol [(-)-3PPP].<sup>[13]</sup>



Scheme 4. Reagents and conditions: a)  $\text{LiAlH}_4$ , THF, 70%; b)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ ,  $\text{EtOAc}$ , 73% (**16**), 91% (**17**); c)  $\text{BH}_3$ , THF, 61% (from **14b**), 70% (from **13a**); d)  $\text{Ca}$ , liquid  $\text{NH}_3$ , then  $\text{Et}_3\text{SiH}$ ,  $\text{TiCl}_4$ , THF, 53%; e)  $\text{AlH}_3$ , THF, 70% (from **9a**), 87% (from **8a**); f)  $\text{HCl}$ ,  $\text{MeOH}$ , then  $\text{H}_2$ ,  $\text{Pd/C}$ , 85%; g)  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{MeOH}$ , 73%; h)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$ ,  $\text{CH}_3\text{CH}_2\text{CHO}$ ,  $\text{EtOAc}$ , 79%; i) aq.  $\text{HBr}$ , 82%.

Simple chiral, aminoalcohol-derived bicyclic lactams that are either unsubstituted at the piperidine carbon atoms or bear an alkyl substituent at the angular C8a position have already been demonstrated to be extremely useful building blocks for the enantioselective construction of a number of natural and non-natural products.<sup>[4, 14]</sup> These syntheses require a later stereocontrolled formation of C–C bonds at the carbon atom positions of the nitrogen heterocycle. Advantageously, the chiral synthons described herein already incorporate the carbon substituents on the heterocyclic ring, thus expanding the potential of chiral bicyclic lactams for the enantioselective synthesis of piperidine derivatives.<sup>[15]</sup> Although the diastereoselectivity of the above cyclodehydrations ranges from only 4:1 to 9:1, taking into account that both enantiomers of phenylglycinol are commercially available and that this auxiliary is easily removable, this method provides a convenient straightforward access to polysubstituted piperidines in both enantiomeric series.

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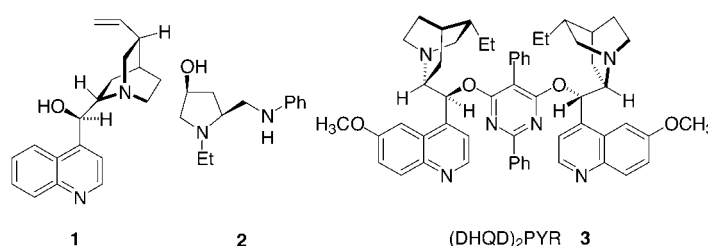
## A Highly Enantioselective and General Conjugate Addition of Thiols to Cyclic Enones with an Organic Catalyst\*\*

Paul McDaid, Yonggang Chen, and Li Deng\*

Enantioselective conjugate addition is a fundamentally important transformation in asymmetric synthesis.<sup>[1]</sup> Catalytic enantioselective conjugate addition to cyclic enones has attracted considerable attention as a general and attractive strategy for the synthesis of optically active cyclic building

blocks. A number of general and highly enantioselective conjugate additions of carbon nucleophiles to cyclic enones catalyzed by transition metals have been reported recently.<sup>[2]</sup> Excellent enantioselectivity has also been obtained in the conjugate addition of carbon nucleophiles to cyclohexenone and  $\alpha,\beta$ -unsaturated aldehydes with organic catalysts.<sup>[3]</sup> However, the development of a general and highly enantioselective 1,4-addition of thiols to cyclic enones remains a challenging goal despite numerous attempts involving metal-based catalysts,<sup>[4]</sup> phase-transfer catalysts,<sup>[5]</sup> and organic catalysts.<sup>[6–11]</sup> We describe here significant progress toward accomplishing this goal using a readily available chiral organic catalyst.

Pioneering studies by Wynberg et al.<sup>[6]</sup> and Mukaiyama et al.<sup>[7]</sup> on the asymmetric 1,4-addition of thiols promoted by organic catalysts pinpointed chiral cyclic amines bearing a  $\beta$ -hydroxy group such as cinchonidine (**1**) and the proline-derived compound **2** as promising catalysts. The highest



enantioselectivities obtained with catalysts **1** and **2** in the conjugate additions of thiols to 5,5-dimethylcyclohexenone and cyclohexenone, respectively, are 75 and 88% *ee*.<sup>[6, 7]</sup> Unfortunately, in additions to other cyclic enones enantioselectivity was found to decrease significantly (<70% *ee*) with either catalyst.<sup>[6, 7]</sup> Since modification or removal of the hydroxy group of catalysts **1** and **2** led to drastically reduced catalyst efficiency, the enantioselective catalysis of **1** and **2** was attributed to a bifunctional mechanism involving the simultaneous activation of the cyclic enone and the thiol by the hydroxy and the amino groups, respectively.<sup>[6, 7]</sup> However, we recently observed that commercially available ethers of mono- and bisquinona alkaloids are more effective than natural cinchona alkaloids as chiral Lewis base catalysts for asymmetric nucleophile–electrophile reactions.<sup>[12]</sup> These observations prompted us to explore the possibility of using a modified cinchona alkaloid to catalyze highly enantioselective 1,4-additions of thiols to cyclic enones.

We first examined natural and modified cinchona alkaloids for their ability to promote enantioselective conjugate addition of thiophenol to cyclohexenone [Eq. (1)]. As illustrated in Table 1, modified cinchona alkaloids bearing no hydroxy groups are comparable to cinchonidine (**1**) in their catalytic activity. Especially notable is that the bis(dihydroquinidinyl)pyrimidine derivative (DHQD)<sub>2</sub>Pyr (**3**) was shown to be more effective than cinchonidine (**1**). Lacking a hydrogen donor, (DHQD)<sub>2</sub>Pyr (**3**) is unable to promote the enantioselective conjugate addition by means of a bifunctional catalysis mechanism similar to that proposed for **1** and **2**.<sup>[6, 7]</sup> Furthermore, reactions promoted by **3**, which was derived from quinidine, gave in excess the *R* isomer of the

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Table 1. Effect of the catalyst on the asymmetric 1,4-addition of thiophenol to cyclohexenone [Eq. (1)].

| Entry | Catalyst <sup>[a]</sup>     | <i>t</i> [h] | Yield [%] <sup>[b]</sup> | <i>ee</i> [%] <sup>[c,d]</sup> |
|-------|-----------------------------|--------------|--------------------------|--------------------------------|
| 1     | quinidine                   | 24           | 81                       | 30 <sup>[e]</sup>              |
| 2     | cinchonidine                | 14           | 90                       | 44                             |
| 3     | DHOD-CLB                    | 4            | 87                       | 10                             |
| 4     | DHOD-PHN                    | 4            | 88                       | 19                             |
| 5     | DHOD-MEQ                    | 2            | 98                       | 22                             |
| 6     | (DHOD) <sub>2</sub> PHAL    | 16           | 91                       | 18                             |
| 7     | (DHOD) <sub>2</sub> AQN     | 23           | 93                       | 21                             |
| 8     | (DHOD) <sub>2</sub> PYR (3) | 19           | 91                       | 53                             |

[a] See Supporting Information for the structures of the catalysts. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] The absolute configuration of the product was determined to be *R* (see Supporting Information). [e] The *S* enantiomer of the product was obtained as the major isomer.

Michael adduct, while the quinidine-promoted reaction generated the *S* isomer as the major product (Table 1). The sense of asymmetric induction of the 1,4-addition of thiophenol to cyclohexenone catalyzed by the modified cinchona alkaloid, with respect to the absolute configuration of C9 and C10 of the cinchona alkaloid skeleton, is therefore opposite to that obtained with natural cinchona alkaloids. This indicates that the corresponding mechanisms for the conjugate additions catalyzed by the modified and natural cinchona alkaloids must differ significantly.

We next turned our attention to the effect of altering the structure of the thiol on the enantioselectivity of the reaction [Eq. (2)]. We found that certain 3- or 4-substituted thiophenols gave substantially improved enantioselectivities (Table 2, entries 5–7 vs entry 1). Interestingly, the (DHOD)<sub>2</sub>PYR-catalyzed conjugate addition of 4-*tert*-butylthiophenol, the best Michael donor for conjugate additions catalyzed by **1**<sup>[6]</sup> and **2**,<sup>[7]</sup> gave poor enantioselectivity (entry 3). The optimal enantioselectivity at room temperature was obtained with the commercially available 2-thionaphthol (entry 8).

Table 2. Asymmetric 1,4-addition of thiols to cyclohexenone catalyzed by (DHOD)<sub>2</sub>PYR (3) [Eq. (2)].

| Entry | RSH | <i>ee</i> [%] <sup>[a]</sup> | Entry | RSH | <i>ee</i> [%] <sup>[a]</sup> |
|-------|-----|------------------------------|-------|-----|------------------------------|
| 1     |     | 53                           | 5     |     | 64                           |
| 2     |     | 21                           | 6     |     | 65                           |
| 3     |     | 30                           | 7     |     | 66                           |
| 4     |     | 41                           | 8     |     | 77 <sup>[b]</sup>            |

[a] Determined by HPLC analysis (see Supporting Information). [b] The absolute configuration of the major enantiomer was determined to be *R* (see Supporting Information).

We were pleased to find that excellent enantioselectivity could be attained for 2-thionaphthol when the reaction was performed at  $-60^{\circ}\text{C}$  with 1.0 mol % catalyst (Table 3, entry 1). Most importantly, excellent enantioselectivities are achieved with a wide range of cyclic enones. Enantiomeric

Table 3. Asymmetric 1,4-addition of 2-thionaphthol to cyclic enones catalyzed by (DHOD)<sub>2</sub>PYR (3).

| Entry            | Enone | <i>T</i> [ $^{\circ}\text{C}$ ] | <i>t</i> [h] | Yield [%] <sup>[a]</sup> | <i>ee</i> [%] <sup>[b]</sup> |
|------------------|-------|---------------------------------|--------------|--------------------------|------------------------------|
| 1                |       | $-60$                           | 17           | 77                       | 94 <sup>[c]</sup>            |
| 2                |       | $-60$                           | 20           | 86                       | 97                           |
| 3                |       | $-60$                           | 30           | 82                       | > 99                         |
| 4                |       | $-60$                           | 48           | 91                       | 97                           |
| 5                |       | $-60$                           | 23           | 55                       | 41                           |
| 6                |       | $-55$                           | 69           | 71                       | 92                           |
| 7 <sup>[d]</sup> |       | $-50$                           | 120          | 88                       | 95                           |
| 8                |       | $-60$                           | 64           | 88                       | 93                           |

[a] Yields of isolated products. [b] Determined by HPLC analysis (see Supporting Information). [c] The absolute configuration of the product was determined to be *R* (see Supporting Information). [d] 1.6 mol % catalyst was employed in this reaction.

excesses ranging from 93 % to greater than 99 % are obtained for six- to nine-membered cyclic enones and various substituted cyclohexenones (Table 3). Although moderate enantioselectivity is obtained with cyclopentenone (entry 5), highly enantioselective conjugate addition is accomplished with 4,4-dimethyl cyclopentenone (entry 6). To our knowledge, there is only one example with 90 % *ee*<sup>[4]</sup> among the reported catalytic asymmetric Michael additions of thiols to cyclic enones.<sup>[1, 4, 6, 7]</sup>

In conclusion, we have realized the first reported general and highly enantioselective catalytic asymmetric 1,4-addition of thiols to cyclic enones which uses an organic catalyst. Our results also extend the scope of chiral Lewis base catalysis by modified cinchona alkaloids to a new class of important reactions. Future studies in our laboratories will focus on elucidating the mechanism of catalysis and expanding the synthetic utility of the reaction.

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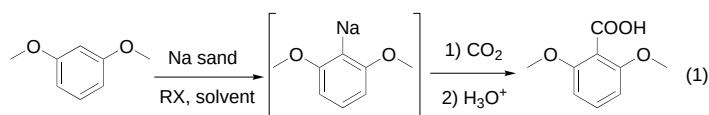
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sodium.<sup>[2–6]</sup> Under classical conditions, organohalides react with sodium to give mainly Wurtz coupling products.<sup>[7, 8]</sup> Moreover, alkylsodium compounds show poor stability, especially in ethereal solvents.<sup>[9, 10]</sup> As a consequence, in spite of the low cost of metallic sodium and the sometimes demonstrated interesting reactivity,<sup>[11]</sup> alkylsodium compounds have not been considered so far as valuable organometallic reagents in organic synthesis.

Herein we report on a straightforward and efficient one-pot *ortho*-metalation procedure relying on the generation of sodiated organic bases from RCl and a stoichiometric amount of metallic sodium in the presence of aromatic substrates.<sup>[12]</sup> Under these conditions, handling and storage of alkylsodium compounds is avoided and *ortho*-metalation is favored over usual coupling and solvolysis side reactions.<sup>[13]</sup>

1,3-Dimethoxybenzene (1,3-DMB), known to undergo *ortho*-metalation with alkyllithium bases in good yields,<sup>[14]</sup> was selected as a model substrate to investigate the scope of the reaction with alkylsodium compounds [Eq. (1)]. Several parameters, including solvent, temperature, and the nature of the organohalide, were varied (Table 1). All reactions were quenched by addition of dry-ice, and the yield of acid [see Eq. (1)] was considered as indicative of the metalation efficiency.<sup>[15]</sup>



## Directed *ortho*-Metalation, a New Insight into Organosodium Chemistry\*\*

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From laboratory to industrial scale, the use of strong organoalkali metal bases is almost exclusively restricted to alkyllithium derivatives.<sup>[1]</sup> They are commercially available as 1–2 M solutions, quite stable and easily generated from alkylhalides and lithium. In contrast, the synthesis of alkylsodium compounds is much more troublesome and requires high-speed mechanical stirring, low temperatures, and excess

Table 1. Influence of some parameters on the directed *ortho*-sodiation of 1,3-DMB [Eq. (1)].<sup>[a]</sup>

| Entry            | RX              | Solvent                  | <i>T</i> [°C] | Yield [%]         |
|------------------|-----------------|--------------------------|---------------|-------------------|
| 1                | 1-chlorooctane  | toluene                  | 20            | 70                |
| 2                | 2-chloropropane | toluene                  | 20            | 8 <sup>[b]</sup>  |
| 3                | 2-bromopropane  | toluene                  | 0             | 21                |
| 4                | chlorobenzene   | toluene                  | 20            | 35 <sup>[c]</sup> |
| 5 <sup>[d]</sup> | 1-chlorooctane  | Et <sub>2</sub> O or THF | 20            | 45 or 86          |
| 6                | 1-chlorooctane  | THF or toluene           | –15           | 30 or 28          |
| 7                | 1-chlorooctane  | toluene                  | 110           | 20                |

[a] The sodium sand was obtained by dispersing melted sodium under vigorous mechanical stirring; see Experimental Section. [b] *T* = room temperature or 0 °C. [c] 2,6-dimethoxybiphenyl was also isolated in 35 % yield.<sup>[16, 17]</sup> [d] Me<sub>2</sub>SO<sub>4</sub> instead of CO<sub>2</sub> used as electrophile.

In the presence of 1-chlorooctane (or 1-chloropropane) 2,6-dimethoxybenzoic acid was obtained in 70 % yield (entry 1), comparable to the yield of classical *n*BuLi metalations.<sup>[14]</sup> When the reaction was conducted in a two-step manner, that is, when the alkylsodium compound was synthesized prior to the addition of 1,3-DMB, only trace amounts (<1 %) of carboxylic acid were detected. The sterically hindered neopentyl chloride did not give any metalation product, and secondary chloroalkanes gave poor results (entry 2).<sup>[3a]</sup> As expected, primary bromoalkanes were too reactive toward sodium, even at low temperature. Yet, secondary bromoalkanes, with a lower tendency to undergo Wurtz coupling, gave the desired acid in moderate yield (entry 3).

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Although alkylsodium compounds react with ethereal solvents much faster than alkyl lithium compounds,<sup>[10]</sup> reaction (1) was efficiently conducted not only in toluene, but also in THF and to a lesser extent in diethyl ether (entries 1 and 5). The thermal instability of alkylsodium compounds<sup>[18]</sup> did not prevent the reaction using melted sodium to give the metalation product in 20 % yield (entry 7). This result emphasizes the exceptional thermal stability of 2,6-dimethoxyphenylsodium. At  $-15^{\circ}\text{C}$ , 2,6-dimethoxybenzoic acid was formed in modest yields (entry 6). In this case, part of the chlorooctane remained unreacted, and no improvement was achieved by increasing the reaction time.

Noteworthy, under optimized conditions, that is, slow addition of 1.2 equiv of pure 1-chlorooctane at room temperature to a mixture of the aromatic substrate and 2.6 equiv of sodium in toluene, the reaction was successfully carried out on a 1-kg scale.

Since only few reports exist on the reactivity of sodiated carbanions the *ortho*-sodiated anion was quenched with various electrophiles. The results proved to be comparable to those reported for conventional commercially available organolithium bases,<sup>[19–23]</sup> with yields ranging from 52 to 86 % (Table 2).

Table 2. Reaction of various electrophiles with 2,6-dimethoxyphenylsodium.

| Entry | Electrophile         | Yield [%] <sup>[a]</sup>                | Entry            | Electrophile                    | Yield [%] <sup>[a]</sup> |
|-------|----------------------|-----------------------------------------|------------------|---------------------------------|--------------------------|
| 1     | DMF                  | 52 (–)                                  | 4                | PhCH <sub>2</sub> Br            | 75 (57 <sup>[21]</sup> ) |
| 2     | B(OMe) <sub>3</sub>  | 70 <sup>[b]</sup> (57 <sup>[19]</sup> ) | 5                | Me <sub>2</sub> S <sub>2</sub>  | 75 (85 <sup>[22]</sup> ) |
| 3     | Me <sub>3</sub> SiCl | 76 (83 <sup>[20]</sup> )                | 6 <sup>[c]</sup> | Me <sub>2</sub> SO <sub>4</sub> | 86 (76 <sup>[23]</sup> ) |

[a] Yields from other publications in brackets. [b] 2,6-Dimethoxyphenylsodium was added dropwise to a trimethylborate solution in toluene. [c] With THF as solvent.

We then tried to extend the scope of our method to other aromatic ethers. 1,2-DMB failed to react under the optimized conditions given above (Table 3, entry 1). Only nonylbenzene arising from solvent metalation was obtained.<sup>[24]</sup> Changing the solvent from toluene to THF resulted in a complex reaction mixture. When 1-chlorooctane was added over a 3 h period to disfavor Wurtz coupling, the yield was brought to 20 % (entry 1). To further favor the heterogeneous reaction, hence the formation of the alkylsodium compound, finely divided micronized sodium was tested.<sup>[25]</sup> Under these conditions, 1,2-DMB underwent clean metalation affording the corresponding carboxylic acid in 80 % yield (entry 2).

Table 3. Sodiation of other substrates in the presence of 1-chlorooctane.

| Entry | Aromatic compound | Sodium dispersion <sup>[a]</sup> | Solvent | Yield [%]             |
|-------|-------------------|----------------------------------|---------|-----------------------|
| 1     | 1,2-DMB           | sand                             | toluene | 0, 20 <sup>[b]</sup>  |
| 2     | 1,2-DMB           | micronized                       | toluene | 80                    |
| 3     | 1,4-DMB           | micronized                       | toluene | 88                    |
| 4     | anisole           | micronized                       | toluene | 25, 45 <sup>[b]</sup> |
| 5     | thiophene         | sand                             | toluene | 90                    |
| 6     | benzofuran        | sand                             | toluene | 85                    |

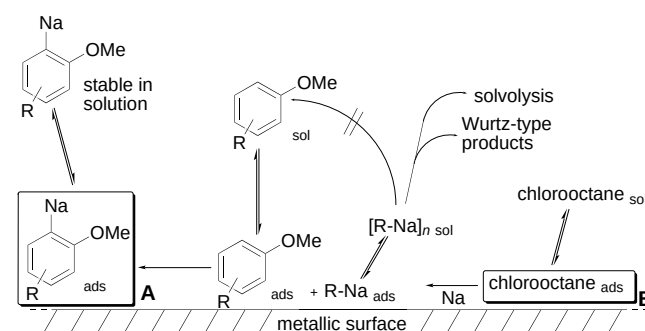
[a] The micronized dispersion in toluene is commercially available from Aldrich. [b] This yield was obtained when diluted 1-chlorooctane was added slowly.

Similar trends were observed with 1,4-DMB and anisole. No acid was formed in toluene or THF until micronized sodium dispersion was used (entries 3 and 4). The slow metalation of anisole might account for the modest 45 % yield obtained.<sup>[26]</sup>

Heterocyclic systems known to easily undergo  $\alpha$ -metalation, such as thiophene and benzofuran, were successfully metalated using sodium sand dispersion (entries 5 and 6).<sup>[27]</sup> Not surprisingly,<sup>[28]</sup> other aromatic compounds bearing electron-withdrawing groups, like oxazolines, secondary and tertiary amides, invariably failed to undergo metalation.<sup>[12b, 29]</sup> In these cases, metallic sodium reacts with the aromatic ring to form complex mixtures even prior to the addition of the chlorooctane.

The three-component heterogeneous *ortho*-metalation presented here involves a complex set of equilibria. The desired path will be followed as soon as the aromatic derivative to be metalated will efficiently trap the in situ formed alkylsodium compound. In other words, the extent of side reactions indebted to the alkylsodium compound, that is homo-coupling and solvolysis, has to be minimized. This holds as long as the substrate bears a readily labile hydrogen as in the case of thiophene or benzofuran (see Table 3, entries 5 and 6). Nevertheless, the substrate acidity alone cannot account for our experimental results as studies by Schlosser and Maggi of the relative rates of the metalation of the DMB isomers with *s*-butyllithium in THF gave the order 1,4- > 1,3- >> 1,2-DMB.<sup>[30]</sup>

1,3-DMB is the only substrate that reacts with the sodium sand dispersion, although 1,4-DMB undergoes proton abstraction with ease. Hence, an additional parameter that influences the whole process has to be taken into account. We believe the *ortho*-metalation step takes place on the metallic surface within the coordination sphere of the alkylsodium molecules progressively formed (Scheme 1), whereby the



Scheme 1. Proposed mechanism for the directed *ortho*-sodiation of aromatic ethers.

substrate is driven onto the surface as a result of its affinity for Na<sup>+</sup>. Literature and our experimental data strongly support this hypothesis. If the abilities of lithiated and of sodiated alkyl bases to coordinate to aromatic ethers are assumed to be similar, anisole binds weakly to an alkylsodium compound whereas 1,3-DMB and an alkylsodium compound form a strong complex.<sup>[31]</sup> 1,3-DMB bears a labile hydrogen and binds Na<sup>+</sup> tightly,<sup>[30, 32]</sup> *ortho*-metalation on the sodium surface will

be highly favored, and the reaction will proceed even with sodium sand. Interestingly, 1,3-DMB forms a strong complex with  $\text{Na}^+$  as the reaction can be successfully carried out in weakly coordinating solvents such as THF or diethylether (Table 1, entries 5 and 6).<sup>[33,34]</sup> In contrast, anisole binds  $\text{Na}^+$  weakly and reacts very slowly with strong bases.<sup>[26]</sup> As a result, the amount of anisole on the sodium sand surface is low, and alkylsodium molecules will be slowly released in the solution. While Wurtz-type products (nonylbenzene and hexadecane) will form in toluene, alkylsodium compounds will decompose rapidly in THF and no *ortho*-metalation is observed.

Since both 1-chlorooctane and anisole compete for the occupation of the metallic surface, complex **A** will more likely form if the specific area of the metal is increased and/or if the chlorooctane concentration is kept negligible, that is, when the amount of **B** is made as low as possible (Scheme 1; Table 3, entry 4).<sup>[35]</sup>

The behavior of 1,2- and 1,4-DMB lies between these two extreme cases; they show intermediate reactivity toward the sodium/alkylchloride metalation system. 1,4-DMB is metalated very efficiently,<sup>[30]</sup> while its affinity for  $\text{Na}^+$  is close to that of anisole. On the other hand, 1,2-DMB coordinates to  $\text{Na}^+$  quite strongly<sup>[32b]</sup> but reacts very slowly with strong bases.<sup>[30]</sup> Low reactivity and low affinity prevent *ortho*-metalation in the presence of sodium sand (Table 3, entry 1). Nevertheless, the reaction proceeds with ease when the specific area of sodium is increased (Table 3, entries 2 and 3).

Besides, the low reactivity of secondary chloroalkanes and the failure of the reaction at low temperature can be ascribed to the fact that the disruption of the sodium particles into smaller aggregates caused by the heat released during the alkylsodium formation is inhibited.<sup>[36]</sup> The formation of secondary alkylsodium compounds is much less exothermic,<sup>[3a]</sup> so the metallic surface is more and more shielded as  $\text{NaCl}$  is progressively formed on it; the result of this is a poor metalation efficiency (Table 1, entries 2 and 6). This hypothesis is corroborated by the unaltered aspect of the sodium dispersion at the end of the reaction.

In conclusion, we have demonstrated that alkylsodium compounds are synthetically useful reagents. Our process requires only inexpensive and readily available reagents. Transportation, storage, and handling of sensitive and dangerous organolithium bases are also avoided. This sodium/chlorooctane-mediated metalation opens new prospects for the metalation of aromatic ethers and heterocycles in laboratories and in the industry.<sup>[37]</sup> Investigations are currently underway to extend the strategy to the metalation of aromatic derivatives containing electron-withdrawing groups.

## Experimental Section

**Preparation of the sodium dispersion:** The quantity of sodium needed was cut off in small pieces from metal sticks, washed with hexane, and immediately added to dry toluene (35 mL per g Na) under inert atmosphere in a three-necked flask equipped with a condenser, a mechanical stirrer and a dropping funnel. The temperature was raised to 110 °C under gentle stirring until the metal fusion was complete (a uniformly bright metal was obtained). The mixture was then cooled to room temperature under vigorous stirring until a finely divided sodium dispersion was obtained. The dispersion usually consisted of small round gray particles of roughly 1 mm size.

**Typical metalation procedure:** The aromatic substrate (1 equiv) was added to the sodium dispersion (2.6 equiv) at room temperature. A small portion (roughly one tenth of 1.3 equiv) of the alkyl halide was added drop-wise to initiate the reaction. The reaction initiated within 2–5 min and was characterized by a slight increase of the temperature. The remaining alkyl halide was then added at constant temperature (if necessary, the reaction was cooled). Metalation was monitored by the slow disappearance of sodium and was usually complete within one to two hours. The electrophile was finally added to the mixture at room temperature and allowed to react for a period ranging from two to ten hours depending on the electrophile.

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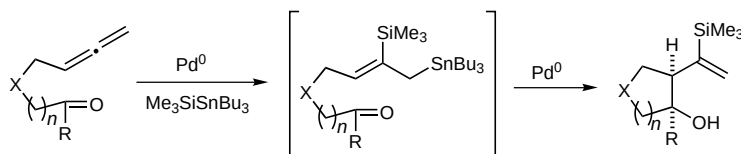
## Palladium-Catalyzed Regio- and Diastereoselective Tandem Silastannylation/Allyl Addition of Allene Aldehydes and Allene Ketones: Synthesis of *cis* Cyclopentanol and Cyclohexanol\*\*

Suk-Ku Kang,\* Young-Hwan Ha, Byung-Soo Ko, Yoongho Lim, and Jihyun Jung

To achieve economically useful transformations in organic synthesis it would be desirable if multistep bond formations and/or bond cleavages could be facilitated with a single catalyst in one pot at a constant temperature. Such a process would minimize the amount of chemicals, the production of waste, and the processing time.<sup>[1, 2]</sup> In this regard, Jeong et al.<sup>[3]</sup> reported allylation/Pauson–Khand reactions with two artificial catalysts in a one-pot procedure. Subsequently, Evans et al.<sup>[4]</sup> developed the allylation/Pauson–Khand reaction in a tandem sequence with a Rh complex as the only catalyst. Recently, Shibasaki and co-workers<sup>[5]</sup> reported a one-pot synthesis of  $\beta$ -cyanohydrin from olefins mediated by a Zr catalyst.

The palladium-catalyzed addition of silylstannanes to allenes is known<sup>[6]</sup> and the palladium- or platinum-catalyzed addition of allylstannanes to aldehydes was reported by Yamamoto et al.<sup>[7, 8]</sup> However, to the best of our knowledge, the transition metal catalyzed addition of allylstannanes to ketones has not yet been successful. Our ongoing studies into the use of allene substrates in organic synthesis<sup>[9]</sup> led us to believe that allene aldehydes and allene ketones are good substrates for palladium-catalyzed silastannylation. In a tandem reaction, the resulting allylstannanes would be good candidates for carbonyl allyl addition with a single palladium catalyst at a constant temperature (Scheme 1).

The results of the tandem silastannylation/carbonyl allyl addition of allene aldehydes and allene ketones to form *cis* cyclopentanol and cyclohexanol<sup>[10]</sup> are summarized in Table 1. In finding



Scheme 1. Tandem silastannylation/allyl addition of allene aldehydes and allene ketones ( $n = 1, 2$ ;  $\text{R} = \text{H}, \text{CH}_3$ ;  $\text{X} = \text{NTs}, \text{O}, \text{C}(\text{CO}_2\text{Et})_2$ , etc.).

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Table 1. The palladium-catalyzed silastannylation/allyl addition of allene aldehydes and allene ketones.<sup>[a]</sup>

| Entry | 1 | 3 | Yield [%]         |
|-------|---|---|-------------------|
| 1     |   |   | 71                |
| 2     |   |   | 66                |
| 3     |   |   | 63                |
| 4     |   |   | 67                |
| 5     |   |   | 66 <sup>[b]</sup> |

[a] The reaction was carried out with  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  (5 mol %),  $\text{Me}_3\text{SiSnBu}_3$  (**2**) (1.1 equiv), and **1** (1.0 equiv) in THF at room temperature for 10 min. [b] The reaction was carried out at room temperature for 80 min.

optimum conditions, it is critical to find an effective palladium catalyst for both silastannylation and carbonyl allyl addition. When allene aldehyde **1a** was treated with trimethylsilylstannane **2** in THF at room temperature in the presence of  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  catalyst for 10 min, *cis* cyclopentanol **3a** was formed in 71 % yield (Table 1, entry 1). Of the palladium and platinum catalysts tested,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ ,  $\text{Pd}_2(\text{dba})_3$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $\text{PtCl}_2(\text{PPh}_3)_2$ ,  $\text{PdCl}_2$ , and  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$ , only  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  in THF at room temperature catalyzed this tandem reaction. At room temperature, the other catalysts did not give any of the cyclized product **3a**. However the reaction of **1a** with silylstannane **2** in the presence of catalytic  $\text{Pd}(\text{PPh}_3)_4$  in THF at reflux for 2 h afforded the cyclized *cis* cyclopentanol **3a** in 53 % yield. The reaction of **1a** with  $\text{Me}_3\text{SiSnBu}_3$  (**2**) in THF for 12 h at room temperature in the presence of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  catalyst gave the cyclized product **3a** (20 %) along with the uncyclized silastannylation product (45 %). The *cis* stereochemistry was confirmed by NOESY (nuclear Overhauser enhancement spectroscopy) experiments together with molecular modeling; the coupling constant ( $J=3.7$  Hz) implies a dihedral angle of  $46^\circ$  for the two protons on the ring junction (see Supporting Information). Under the same conditions,  $\delta$ -allene aldehyde **1c** cyclized smoothly to give substituted cyclopentanol **3d** in 63 % yield (Table 1, entry 3). This tandem sequence was also applied to allene ketones.  $\delta$ -Allene ketone **1d** was treated with  $\text{Me}_3\text{SiSnBu}_3$  (**2**) in the presence of  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  catalyst under the same conditions to afford the methyl-substituted *cis* cyclopentanol **3d** in 67 % yield (Table 1, entry 4). To the best of our knowledge, this is the first

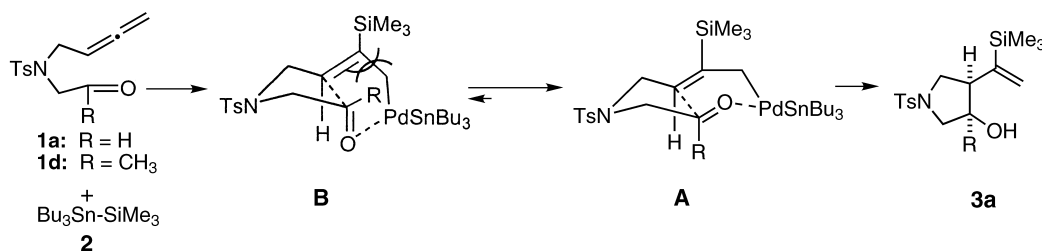
example of a palladium-catalyzed allyl addition of organostannanes to ketones, although it is known for aldehydes.<sup>[7]</sup> The *cis* stereochemistry of **3d** was unambiguously determined by NOE interactions between the methyl protons and the proton at the ring junction (2.5 % enhancement). Under the same conditions, the malonate-substituted  $\delta$ -allene ketone **1e** was converted into the *cis*-cyclopentanol **3e** (66 % yield) after a prolonged reaction time (Table 1, entry 5).

This silastannylation/allyl addition tandem reaction was extended to synthesize cyclohexanol derivatives **5** (Table 2). Allene aldehyde **4a** was treated with  $\text{Me}_3\text{SiSnBu}_3$  (**2**) in the presence of  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  to afford *cis*-cyclohexanol **5a** in 62 % yield (Table 2, entry 1). Allene aldehyde **4c** was converted into diester-substituted cyclohexanol derivative **5c** (63 % yield) under the same conditions, but with a 2-h reaction time (Table 2, entry 3). Allene aldehyde **4d** was smoothly cyclized in a tandem reaction to provide pyranyl-substituted alcohol **5d** in 68 % yield (Table 2, entry 4). The *cis*

Table 2. The palladium-catalyzed silastannylation/allyl addition of allene aldehydes and allene ketones.<sup>[a]</sup>

| Entry | 4 | Product | Yield [%]         |
|-------|---|---------|-------------------|
| 1     |   |         | 62                |
| 2     |   |         | 64                |
| 3     |   |         | 63 <sup>[b]</sup> |
| 4     |   |         | 68                |
| 5     |   |         | 67                |
| 6     |   |         | 65 <sup>[c]</sup> |

[a] The reaction was run with  $(\pi\text{-allyl})_2\text{Pd}_2\text{Cl}_2$  (5 mol %),  $\text{Me}_3\text{SiSnBu}_3$  (**2**) (1.1 equiv), and allene-aldehyde or ketone **4** (1.0 equiv) in THF at room temperature for 10 min. [b] The reaction was carried out at room temperature for 2 h. [c] The reaction was carried out at room temperature for 70 min.



Scheme 2.

stereochemistry of **5d** was deduced clearly by means of X-ray crystallography. This tandem cyclization was also applied to allene ketones. Thus allene ketone **4e** was cyclized to give piperidyl-substituted alcohol **5e** in 67% yield (Table 2, entry 5). However, the malonate substrate **4f** gave rise to *cis*-cyclohexanol **5f** (30%) as well as the simple addition product **6** (35%) (Table 2, entry 6).

The exact mechanism of this *cis*-stereoselective tandem reaction has yet to be elucidated. It is presumed that Me<sub>3</sub>SiPdSnBu<sub>3</sub> adds initially to the allene moiety to give  $\sigma$ - or  $\pi$ -allyl palladium complexes, which undergo intramolecular carbonyl allyl addition to afford *cis*-cycloalkenols. The *cis* selectivity of the reaction can be ascribed to the fact that intermediate **A**, which leads to the *cis*-cyclopentanol, is energetically more stable than **B**, presumably because of the steric hindrance between TMS and R (R = H, Me) groups (Scheme 2).<sup>[11]</sup>

In summary, the palladium-catalyzed regio- and diastereoselective tandem silastannylation/carbonyl allyl addition of allene aldehydes and ketones gives rise to *cis*-cycloalkenols. The process requires a single catalyst and is carried out at constant temperature.

## Experimental Section

Typical procedure: trimethyl(tributylstannyl)silane **2** (150 mg, 0.41 mmol) was added to a stirred solution of **1a** (100 mg, 0.38 mmol) and ( $\pi$ -allyl)<sub>2</sub>PdCl<sub>2</sub> (6.9 mg, 5 mol %) in THF (3 mL). The reaction mixture was stirred room temperature for 10 min, and the THF solvent was evaporated *in vacuo*. The crude product was separated by means of column chromatography (EtOAc/hexane 1:2) to afford the cyclized product **3a** (91 mg, 71%) as a white solid. M.p. 95 °C; *R*<sub>f</sub> = 0.41 (EtOAc/hexane 1:2); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.00 (s, 9H), 2.35 (s, 3H), 2.89 (m, 1H), 3.29 (dd, 1H, *J* = 9.3, 11.3 Hz), 3.35 (d, 1H, *J* = 11.5 Hz), 3.40 (dd, 1H, *J* = 7.2, 9.3 Hz), 4.05 (m, 1H), 5.59 (d, 2H, *J* = 1.3 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.0 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 147.9, 145.0, 135.7, 131.2, 129.7, 129.1, 72.2, 57.7, 50.1, 49.8, 23.1, 0.0; HR-MS: calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>Si: 339.1324, found: 339.1366.

Typical experimental procedures for the preparation of **1a**, **1c**–**1e**, **4c**–**4f**, **3a**, spectroscopic and analytical data for **1a**–**1e**, **4a**–**4f**, **3a**–**3e**, **5a**–**5f**, **6**, and X-ray crystallographic data of **5d** can be found in the Supporting Information.

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## IAN-Amines: Direct Entry to a Chiral C<sub>2</sub>-Symmetric Zirconium(IV) $\beta$ -Diketimine Complex\*\*

Sarah B. Cortright and Jeffrey N. Johnston\*

The immense utility of metallocene-based catalysts for synthesis<sup>[1]</sup> has stimulated the development of non-metallocene complexes that conserve metallocene topographies but offer a greater degree of accessibility and/or improved performance.<sup>[2]</sup> A number of recent publications have demonstrated that amidinate ligands,<sup>[3,4]</sup>  $\beta$ -diketimines,<sup>[5–7]</sup> and other variations on the [1,*n*]-bisimine template are promising in this regard for group IV metals. In general, ligands used as the basis for a non-metallocene complex must 1) bind to the

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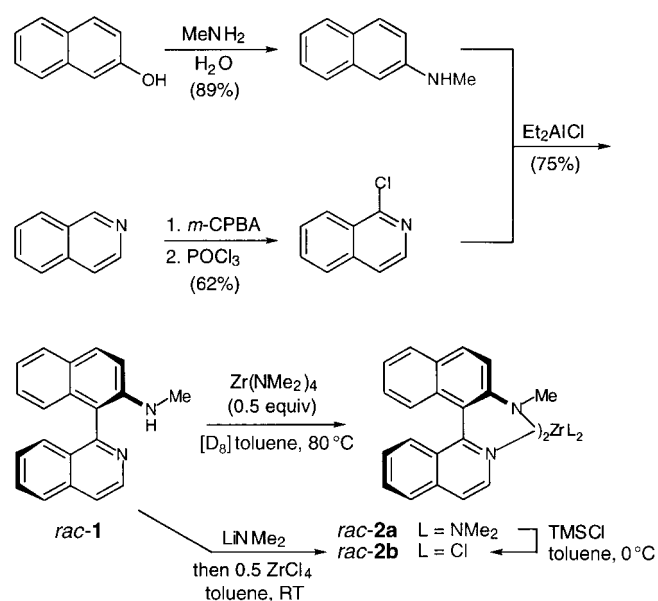
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metal organizational center in a manner of high symmetry while 2) leaving the metal with substantial (catalytic) reactivity.<sup>[8]</sup>

Chiral  $\beta$ -diketimine **1** (see Scheme 1) and related derivatives are conspicuously absent from the literature<sup>[9]</sup> despite the similarity to countless binaphthyl-based ligands that have proven broadly useful in metal-mediated asymmetric synthesis.<sup>[10]</sup> As a potential bidentate ligand, this class of  $\beta$ -diketimines is particularly interesting since the usually non-planar binaphthyl backbone prevents a full resonance interaction observed in most  $\beta$ -diketimines. However, the attenuation of resonance and the associated electronic differentiation of the ligating nitrogen atoms might be used to achieve stereocontrol in metal complexation. In this initial report we describe the synthesis of the first two members (**1** and **3**) of this class of amine ligands derived from Isoquinoline and 2-Amino Naphthalene—IAN-amines.<sup>[11]</sup> A highly diastereoselective 2:1 complex formation between *rac*-**1** and zirconium(IV) to form a monomeric  $C_2$ -symmetric zirconium(IV) complex is also documented and constitutes a significant advance on the first criterion stated above.

Convergence and expense were two guiding factors in the synthesis development for **1**. Hence, Bucherer reaction of 2-naphthol with aqueous methyl amine in a sealed tube provided 2-methylamino naphthalene in 89% yield as a brown liquid.<sup>[12]</sup> 1-Chloroisoquinoline was prepared from isoquinoline according to literature precedent by exposure to *m*-chloroperbenzoic acid (*m*-CPBA) and phosphorus oxychloride (Scheme 1).<sup>[13]</sup>



Scheme 1. Synthesis of ligand *rac*-**1** and zirconium complexes *rac*-**2**.

A variety of coupling methods were then investigated. In general, metalation of the amine prior to its addition to a solution of 1-chloroisoquinoline provided only the product of C–N-coupling. Unfortunately, this behavior was found to be independent of solvent and counterion. Similarly, Lewis acids of varying strength and structure failed to deliver the desired C–C-coupled product **1**. Fortunately, diethyl aluminum chlor-

ide was effective and furnished the biaryl amine consistently in 75% yield. Unreacted 2-methylamino naphthalene and 1-chloroisoquinoline could be recovered quantitatively and recycled. Although we continue to optimize this convergent synthesis route, the target amine is easily accessed on multi-gram scale with intermediates that are either crystalline solids or distillable liquids.

In order to indirectly examine the barrier to atropisomerization for **1**,<sup>[14]</sup> diastereomeric  $\alpha$ -methylbenzylamine derivatives **3** were synthesized, separated by silica gel chromatography, and their thermal integrity independently examined (Table 1). The diastereomers were indefinitely stable to

Table 1. Thermal atropisomerization of enantiopure (*S*)- $\alpha$ -methylbenzyl IAN-amines **3**.

| Entry | Conditions<br><b>3a/3b</b> | Relative ratio <sup>[a]</sup> |
|-------|----------------------------|-------------------------------|
| 1     | toluene, 110 °C, 4 h       | 100:0                         |
| 2     | xylenes, 145 °C, 5 h       | 67:33                         |
| 3     | xylenes, 145 °C, 17 h      | 50:50                         |

[a] Reactions monitored by removing an aliquot from the reaction mixture and examination of the product ratio by 400 MHz <sup>1</sup>H NMR after solvent removal. Relative configurations of the diastereomers are arbitrarily assigned. Identical ratios observed when beginning from either **3a** or **3b** (>95:5).

prolonged refluxing in toluene. It was not until 145 °C that atropisomerization was observed to the extent of 67:33 after 5 hours. Both **3a** and **3b** equilibrated at indistinguishable rates to a 50:50 diastereomeric mixture upon prolonged heating at this temperature, which suggests that it is unlikely that the atropisomerization barrier was significantly affected by the benzylic chiral center. By analogy, **1** is expected to be configurationally stable to a reasonably high temperature.

The complexation of **1** ( $C_1$ -symmetry) to  $Zr^{IV}$  was next examined with the hope of obtaining a 2:1 complex of high symmetry based on the analysis provided above. In principle, there are five possible diastereomeric 2:1 complexes in which the two ligands are heterochiral, whereas eight complexes can form with two homochiral ligands. Hence, when using *rac*-**1** in the transformation **1**  $\rightarrow$  **2**, thirteen diastereomeric complexes are possible.

In the event, *rac*-**1** and zirconium tetrakis(dimethylamide) were combined in a 2:1 ratio in  $[D_8]$ toluene. When the resulting red solution was examined by <sup>1</sup>H NMR spectroscopy, complete formation of the 1:1 complex was observed. The solution was then heated to 80 °C in a sealed tube for 12 hours. <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy revealed the quantitative formation of a single diastereomeric complex in agreement with *rac*-**2**. Orange needles suitable for X-ray diffraction<sup>[15]</sup> were grown from the reaction mixture and the structure was solved as depicted in Figure 1.<sup>[16]</sup>

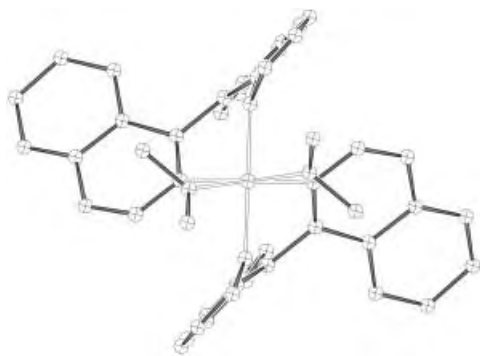


Figure 1. ORTEP diagram of *rac*-**2a** displaying  $C_2$ -symmetry (front view).

Only one 2:1 diastereomeric complex is observed spectroscopically regardless of reaction temperature and time, which suggests that isomerization through amine elimination is not operative.<sup>[17]</sup> At present, we cannot fully discount ligand atropisomerization on-metal but are encouraged by our studies of ligand atropisomerization and the lack of intermediates identifiable by NMR spectroscopy during formation of **2**.<sup>[18]</sup> It is also significant to note that separate 1:1 complexes formed from **3a** and **3b** with  $Zr(NMe_2)_4$  did not atropisomerize during prolonged heating at 90 °C. That the  $C_2$ -symmetric complex is likely the kinetic product is further supported by formation of the same dichloride complex (*rac*-**2b**) by either treatment of *rac*-**2a** with trimethylsilyl chloride (TMSCl), or addition of the lithium salt of *rac*-**1** to zirconium(IV) chloride at room temperature.<sup>[19]</sup> Orange single crystals of *rac*-**2b** were obtained and subjected to X-ray analysis (Figure 2).<sup>[20]</sup>

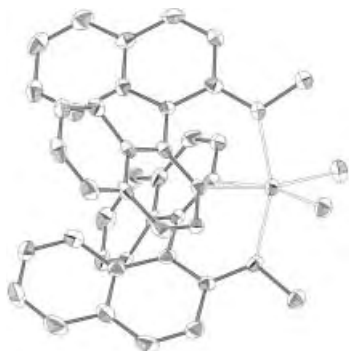


Figure 2. ORTEP diagram of *rac*-**2b** displaying distorted octahedral zirconium coordination geometry (side view).

Several observations are evident from the data.<sup>[21]</sup> The most striking feature is the selection of identical ligand antipodes by the metal. The *cis* arrangement of both pyridyl and dimethylamido nitrogen atoms mandates a *trans* arrangement for the anilinic nitrogen atoms. The binaphthyl backbone renders the  $\beta$ -diketimine nonplanar, which results in electronic differentiation of the chelating atoms. Therefore, **1** is better viewed chemically as a  $\beta$ -amido Schiff base.

The favored metal diastereomer possesses the highly desirable  $C_2$ -symmetry<sup>[5]</sup> characteristic of many effective metal catalysts used in asymmetric synthesis.<sup>[1]</sup> The location of the chelating amido atoms at apical sites of the distorted

octahedron provides the opportunity for steric manipulation above and below the plane of the *cis*-dimethylamido substituents. Additional steric demand is imposed by the isoquinoline rings in opposing quadrants about the metal center.

IAN-Amines are a class of configurationally stable axially chiral  $\beta$ -diketimines that provide direct access to  $C_2$ -symmetric non-metallocene group IV metal complexes. These complexes are remarkably similar, yet truly complementary to the metallocenes by topographical comparison. The high degree of order and symmetry observed in complexation of **1** compares favorably to the traditional use of single polydentate ligands to craft  $C_2$ -symmetric coordination space.<sup>[22]</sup>

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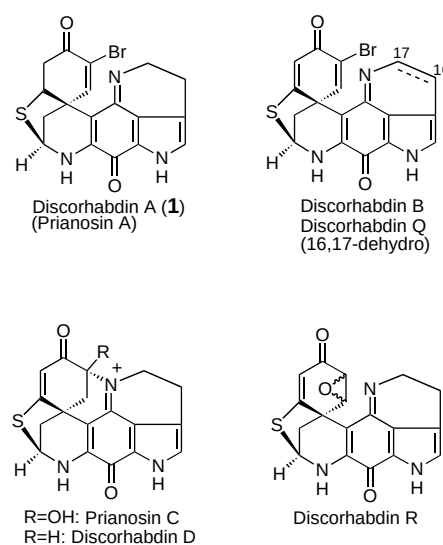
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- [16] Crystal data for *rac-2a*: crystal dimensions  $0.30 \times 0.10 \times 0.03$  mm, monoclinic, space group  $C2c$ ,  $a = 21.404(4)$ ,  $b = 12.253(3)$ ,  $c = 18.103(4)$  Å,  $\beta = 96.27(3)^\circ$ ;  $V = 4719.58$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho = 1.160$  mg mm<sup>-3</sup>;  $\mu = 0.71073$  mm<sup>-1</sup>,  $F(000) = 1720$ , Bruker Smart6000 CCD diffractometer,  $1.92 < \theta < 26.37^\circ$ ,  $\text{MoK}\alpha$  radiation,  $\lambda = 0.71073$  Å,  $\Omega$  scans,  $T = 112(2)$  K, 36868 reflections measured, 4813 unique, 1668 with  $I > 2\sigma(I)$ ,  $-26 \leq l \leq 25$ ,  $-15 \leq k \leq 14$ ,  $-22 \leq h \leq 22$ ;  $R = 0.0667$ ,  $wR = 0.0644$ ,  $\text{GOF} = 1.565$ ,  $\Delta\rho_{\text{max}} = 0.31$  e Å<sup>-3</sup>.
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- [20] Crystal data for *rac-2b*: crystal dimensions  $0.15 \times 0.12 \times 0.10$  mm, monoclinic, space group  $P2_1/c$ ,  $a = 20.4685(12)$ ,  $b = 17.3030(10)$ ,  $c = 21.1452(13)$  Å,  $\beta = 118.062(2)^\circ$ ;  $V = 6608.52$  Å<sup>3</sup>,  $Z = 8$ ,  $\rho = 1.465$  mg mm<sup>-3</sup>;  $\mu = 0.71073$  mm<sup>-1</sup>,  $F(000) = 2976$ , Bruker Smart6000 CCD diffractometer,  $2.24 < \theta < 27.50^\circ$ ,  $\text{MoK}\alpha$  radiation,  $\lambda = 0.71073$  Å,  $\Omega$  scans,  $T = 111$  K, 48532 reflections measured, 15184 unique, 6638 with  $I > 2\sigma(I)$ ,  $-24 \leq l \leq 26$ ,  $-21 \leq k \leq 22$ ,  $-27 \leq h \leq 23$ ;  $R = 0.0322$ ,  $wR = 0.0241$ ,  $\text{GOF} = 0.627$ ,  $\Delta\rho_{\text{max}} = 0.36$  e Å<sup>-3</sup>.
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## Synthetic Studies on the Sulfur-Cross-Linked Core of Antitumor Marine Alkaloid, Discorhabdins: Total Synthesis of Discorhabdin A\*\*

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Discorhabdins and prianosins have been isolated from marine sponges such as New Zealand sponges of the genus *Latrunculia*, Okinawan sponge *Prianos melanos*, and Fijian sponge *Zyzzya cf. Marsailis*. Among the various discorhabdins (A–R) isolated, discorhabdins A (**1**),<sup>[1a,b,d]</sup> B,<sup>[1b]</sup> D,<sup>[1c]</sup> Q,<sup>[1e]</sup> and R<sup>[1f]</sup> have a unique sulfur-containing fused-ring system incorporating an azacarbocyclic spirocyclohexadienone and a pyrroloiminoquinone system (Scheme 1), and show potent antitumor activity.<sup>[2]</sup> The discorhabdins have



Scheme 1. Sulfur-containing discorhabdins.

attracted the synthetic interest of several groups including ours because of their cytotoxicity and unusual ring structures.<sup>[3]</sup> However, to the best of our knowledge, the total syntheses of sulfur-containing discorhabdins have not yet been reported because construction of the labile and highly strained *N,S*-acetal (sulfur-cross-linked) core was difficult. Furthermore, the timing and insertion point for the introduc-

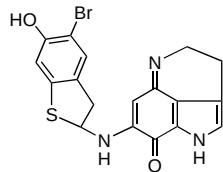
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tion of sulfur in discorhabdins have not yet been clarified biosynthetically.<sup>[4]</sup>

We report herein synthetic studies on the sulfur-cross-linked spirodienone core of discorhabdin alkaloids, which results in the first total synthesis of (±)-discorhabdin A (**1**).

First, on the basis of a plausible hypothesis by Munro and co-workers,<sup>[4]</sup> we examined the biosynthetically potential route from makaluvamine F (**2**)<sup>[1d, 3h]</sup> using our previously

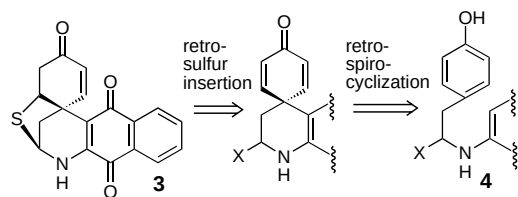


Makaluvamine F (**2**)

developed oxidative spirocyclization reaction with phenyliodine(III) bis(trifluoroacetate) (PIFA).<sup>[3d, 5]</sup>

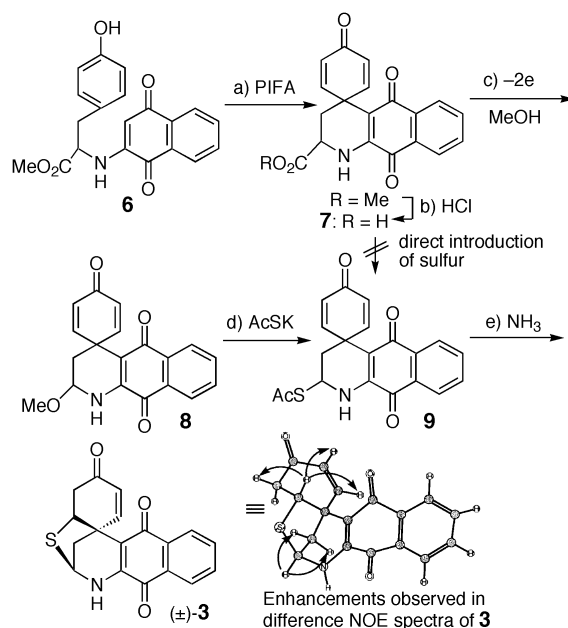
The spirocyclization of **2** using PIFA under various conditions yielded a complex mixture. We also examined the formation of a spirodienone from **2** using the CuCl<sub>2</sub>/NEt<sub>3</sub>/O<sub>2</sub> system developed by Au-

bart and Heathcock,<sup>[3i]</sup> but obtained a complex mixture. Therefore, we altered the synthetic strategy. Retrosynthetic analysis of the highly strained core of **1**, namely, the sulfur-cross-linked spiro-fused ring system **3**, is outlined in Scheme 2. Key elements of our strategy include the iodine(III)-induced oxidative spirocyclization of **4** and the final introduction of the sulfur group leading to the cross-linked core.



Scheme 2. Retrosynthetic analysis of sulfur-cross-linked core (**3**) of discorhabdin A.

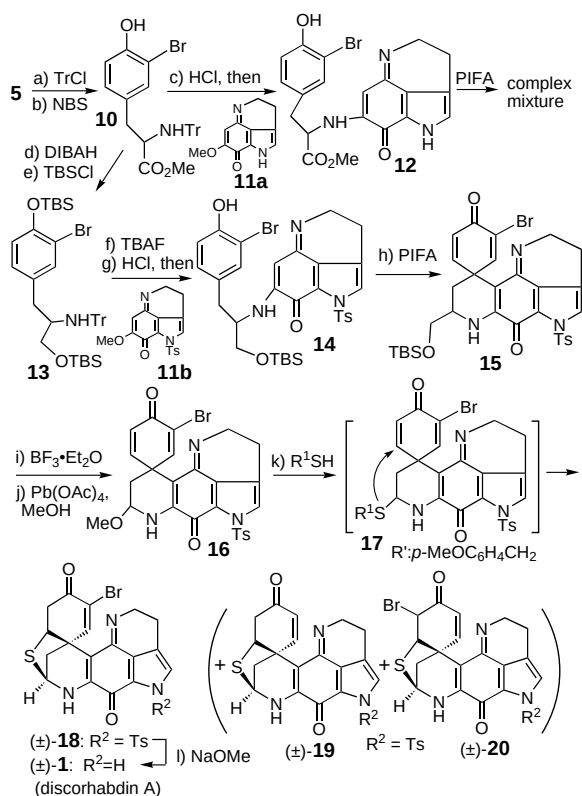
We set out to explore the feasibility of constructing the sulfur-cross-linked core of discorhabdins using aminonaphthoquinone **6** as a model substrate. Compound **6** was readily prepared from commercially available (L)-tyrosine methyl-ester (**5**) and 1,4-naphthoquinone (Scheme 3). Oxidative spirocyclization of **6** using PIFA/montmorillonite K10 (MK10), followed by acid hydrolysis (6N HCl/dioxane-H<sub>2</sub>O) yielded the corresponding spirodienone carboxylic acid **7**. The use of MK10<sup>[6]</sup> improved the yield of this spirocyclization step compared to our previous procedure.<sup>[3d, 5]</sup> We then attempted the direct introduction of a sulfur functional group by oxidative decarboxylation of **7** in the presence of several thiols or AcSH. However, **7** was mostly recovered because of the high reactivity of sulfur nucleophiles towards oxidants and anodic oxidation. Thus, we examined an alternative route via *N,O*-acetal **8**, which could be readily prepared by oxidative decarboxylation of **7**. Consequently, the anodic oxidation<sup>[7]</sup> (graphite anode/graphite cathode system in a nondivided cell) of **7** proceeded smoothly in MeOH in the presence of 5 mol % NaOMe to give **8** in 60% yield. In contrast, chemical oxidation reactions using Pb(OAc)<sub>4</sub>, PhI(OAc)<sub>2</sub> (PIDA), or PIFA afforded **8** only in low to moderate yields. After an extensive survey of sulfur nucleophiles, such as AcSR (R = H, TMS, K), EtOCS<sub>2</sub> K, M<sub>2</sub>S (M = Li, Na, Me<sub>3</sub>Si), TrSH,



Scheme 3. Construction of sulfur-cross-linked core **3**. a) PIFA-MK 10, CF<sub>3</sub>CH<sub>2</sub>OH, 0.5 h, 42%; b) 6M aq HCl, 1,4-dioxane, 60 °C, 2.5 h, 76%; c) -2e, NaOMe (5 mol %), MeOH, 60% (Pb(OAc)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 45%; PhI(OAc)<sub>2</sub>, MeOH, 22%; PIFA, MeOH, 29%); d) AcSK-BF<sub>3</sub>·Et<sub>2</sub>O, THF, -78 → 4 °C, 24 h, 78%; e) 2M NH<sub>3</sub>/EtOH, 12 h, 51%.

PhCOSH, and *t*BuSH, which may convert the methoxy group of **8** into a sulfur group, the thioacetyl group was introduced efficiently using AcSK in the presence of BF<sub>3</sub>·Et<sub>2</sub>O to give **9** in 78% yield. Several thiol groups could also be substituted in low to moderate yields. Treatment of **9** with 2M NH<sub>3</sub> in EtOH yielded the sulfur-cross-linked compound (±)-**3** in 51% yield (Scheme 3). The structural features of **3** were supported by spectroscopic data<sup>[8]</sup> and was compared with the data reported for **1** by Munro and co-workers.<sup>[1b]</sup> The three-dimensional structure of **3** was deduced from difference NOE spectra recorded in (CD<sub>3</sub>)<sub>2</sub>SO. The observed enhancements (Scheme 3) were in complete agreement with structure **3**.

Thus, we applied this model study to the total synthesis of discorhabdin A. We first examined the same path as that towards the naphthoquinone model compound **3**. Tritylation of **5** followed by monobromination with NBS yielded **10** in 65% yield (2 steps; Scheme 4). A coupling reaction of **10** with pyrroloiminoquinone **11a**, which was prepared by our previously developed PIFA-induced pyrroloiminoquinone formation,<sup>[9]</sup> provided **12** in 46% yield. We then examined the oxidative spirocyclization reaction of **12** using PIFA. Although various reaction conditions were tested, this reaction did not give the corresponding spirodienone, but unexpectedly yielded a complex mixture. Thus, we modified the synthetic strategy as follows: reduction of **10** with DIBALH followed by silylation of the resulting alcohol with TBSCl gave the bisilylated compound **13**. Selective desilylation of **13** with TBAF in THF, followed by a coupling reaction with 1-tosylated pyrroloiminoquinone derivative **11b** yielded **14**. Spirodienone formation using PIFA proceeded effectively in the presence of MK10 to give **15** as a mixture of two diastereomers in 45% yield.



Scheme 4. Total synthesis of discorhabdin A (**1**). a) TrCl, Et<sub>3</sub>N, DMF, quant.; b) NBS, DMF, 65%; c) 0.1N HCl/MeOH, then **11a**, MeOH, 20 h, 46%; d) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C → RT, 5 h, 96%; e) TBSCl, DBU, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1.5 h, 87%; f) TBAF, THF, 0 °C, 0.5 h, quant.; g) 0.1N HCl/MeOH, then **11b**, MeOH, 16 h, 54%; h) PIFA-MK 10, CF<sub>3</sub>CH<sub>2</sub>OH, 0.5 h, 45%; i) BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → RT, 7 h, 90%; j) Pb(OAc)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (2/1), 0 °C, 1.5 h, 88%; k) *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>SH, 30% HBr-AcOH, CH<sub>2</sub>Cl<sub>2</sub>, -78 → -4 °C, 15 h, **18** (22%), **19** (19%), **20** (13%); l) NaOMe, THF-MeOH, 0 °C, 1 h, 65%. Tr = triphenylmethyl; NBS = *N*-bromosuccinimide; DIBALH = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAF = tetrabutylammonium fluoride; Ts = toluene-4-sulfonyl.

The diastereomeric mixture **15** was desilylated, and then converted into the methoxy compound **16** by oxidative dealkylation with Pb(OAc)<sub>4</sub>. The remaining challenge was to transform *N,O*-acetal **16** to *N,S*-acetal **17** because of the instability of **16** towards both acidic and basic reaction conditions. We first examined the introduction of a thioacetyl group, and applied the best method for the preparation of a model compound **9** to compound **16**. However, **17** (R<sup>1</sup> = Ac) was not obtained at all, but instead a complex mixture was yielded. Thus, we re-investigated various sulfur nucleophiles, such as Na<sub>2</sub>S, (R<sub>3</sub>Si)<sub>2</sub>S, TrSH, (*p*-MeO)BnSH, and *t*BuSH to obtain **17**. As a result, a *p*-methoxybenzylthiol group was introduced efficiently in the presence of BF<sub>3</sub>·Et<sub>2</sub>O to give **17**. Debenzylation of **17**, a labile and highly functionalized compound, also required the mildest possible reaction conditions. Our initial strategy was to perform a mild debenzylation on the *p*-methoxybenzylsulfonium salt formed by 1,4-addition of a sulfide group. Accordingly, we treated **17** with 30% HBr-AcOH followed by workup with NaHCO<sub>3</sub> but obtained only a trace amount of *N*-tosylated discorhabdin A (**18**). Ultimately, we found an efficient one-pot transformation procedure yielding **18** in 22% yield from **16**. The procedure

used *p*-methoxybenzylthiol in 30% HBr-AcOH followed by treatment with aqueous MeNH<sub>2</sub> and gave **18**<sup>[10]</sup> as well as the undesired debrominated compounds **19** and **20**, which were formed by 1,4-addition to the bromo-enone side. Removal of the Ts group of **18** with NaOMe provided (±)-discorhabdin A (**1**) in 65% yield (Scheme 4).

The spectral data of synthetic **1** was identical to those reported for the natural product.<sup>[1a,b]</sup> Further improvement of the overall yield and an investigation into the total synthesis of optically active discorhabdin A are now underway.

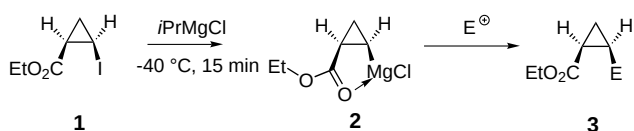
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- Characterization of (±)-**3**: orange solid; *R*<sub>f</sub> = 0.20 (silica gel, *n*-hexane/AcOEt 2/1); m.p. 255–257 °C (from AcOEt); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 8.07 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 10.5 Hz, 1H), 6.49 (brs, 1H), 6.19 (d, *J* = 10.5 Hz, 1H), 5.29–5.33 (m, 1H), 4.60 (dd, *J* = 12.0, 7.5 Hz, 1H), 2.61–2.83 (m, 4H); <sup>13</sup>C NMR (75.5 MHz, [D<sub>6</sub>]DMSO, 25 °C): δ = 195.7, 180.6, 178.4, 154.9, 144.9, 135.0, 133.0, 132.4, 129.8, 125.7, 125.4, 124.9, 118.8, 59.5, 55.7, 46.8, 45.3, 39.4; IR (KBr): ν̄ = 1680, 1675, 1595, 1565, 1495 cm<sup>-1</sup>; UV/Vis (MeOH): λ<sub>max</sub> (ε) = 473 (1300), 270 (10900), 245 nm (10000); HR-MS: calcd for C<sub>18</sub>H<sub>13</sub>NO<sub>3</sub>S [M<sup>+</sup>]: 323.0616, found: 323.0621.
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- Characterization of (±)-**18**: red solid; *R*<sub>f</sub> = 0.70 (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 40/1); m.p. > 300 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 25 °C, TMS): δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.93 (d, *J* = 3.9 Hz, 1H), 5.28 (t, *J* = 3.9 Hz, 1H), 4.62 (dd, *J* = 11.7, 7.8 Hz, 1H), 4.29 (dt, *J* = 18.3, 6.0 Hz, 1H), 3.89 (dt, *J* = 18.3, 9.0 Hz, 1H), 2.80–2.86 (m, 2H), 2.61–2.77 (m, 4H), 2.42 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 25 °C): δ = 188.0, 168.3, 154.8, 152.8, 146.0, 140.6, 134.5, 129.8, 128.7, 126.1, 125.1, 121.9, 119.6, 118.4, 116.2, 61.3, 55.9, 50.0, 50.0, 45.5, 39.9, 21.7, 17.7; IR (KBr): ν̄ = 3365, 1680, 1660, 1610, 1595, 1565, 1525, 1455, 1375 cm<sup>-1</sup>; UV/Vis (CHCl<sub>3</sub>): λ<sub>max</sub> (ε) = 483 (1400), 326 (12200), 265 (14400), 242 nm (18200); HR-FAB-MS: calcd for C<sub>25</sub>H<sub>21</sub>BrN<sub>3</sub>O<sub>4</sub>S<sub>2</sub> [M+H<sup>+</sup>]: 570.0157, found: 570.0171.

# Preparation of New Functionalized Cyclopropylmagnesium Reagents\*\*

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Functionalized organometallic compounds are important reagents for the preparation of complex polyfunctional molecules.<sup>[1]</sup> Recently, we have shown that polyfunctional aryl-, heteroaryl-, and alkenylmagnesium halides can be readily prepared by using an iodine–magnesium exchange reaction.<sup>[2,3]</sup> Herein, we report the preparation of the first functionalized cyclopropylmagnesium<sup>[4]</sup> reagents bearing an ester group, as well as the stereoselective preparation of functionalized cyclopropylmagnesium carbenoids.<sup>[5]</sup> The iodine–magnesium exchange is a fast reaction with aromatic iodides bearing electron-withdrawing groups, however, it is considerably slower with alkyl iodides where competitive substitution and elimination reactions can occur. Therefore, we have directed our first investigations towards cyclopropane derivatives where substitution and elimination side reactions are difficult.<sup>[6]</sup> Thus, the readily available 2-iodocyclopropanecarboxylate<sup>[7]</sup> **1** was treated with *i*PrMgCl (1.1 equiv) in THF at  $-40^{\circ}\text{C}$  for 15 min and afforded the corresponding *cis*-cyclopropylmagnesium chloride **2** (Scheme 1). This reagent shows excellent stability as a consequence of the presence of the ester group which has stabilizing chelating and inductive effects.<sup>[8]</sup> Compound **2** can be trapped with retention of configuration by a range of electrophiles either directly (reaction with  $\text{Me}_3\text{SnCl}$ , PhSSPh, toluene-4-sulfonyl cyanide (TosCN),<sup>[9]</sup> or aldehydes) or after catalytic transmetalation to copper (reaction with allylic bromides and chlorides)<sup>[10]</sup> or palladium (reaction with functionalized aryl iodides) to give products of type **3** (Scheme 1 and Table 1).



Scheme 1. Synthesis of a functionalized cyclopropylmagnesium reagent by an iodine–magnesium exchange.

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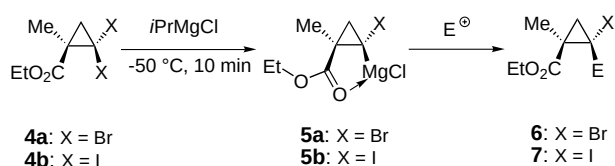
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Table 1. Reactions of functionalized magnesium reagents **2**, **5a**, and **5b** with electrophiles that lead to products of type **3**, **6**, and **7**.

| Entry | Grignard reagent | Electrophile                    | Product of type <b>3</b> or <b>6</b> | Yield [%] <sup>[a]</sup> |
|-------|------------------|---------------------------------|--------------------------------------|--------------------------|
| 1     | <b>2</b>         | $\text{Me}_3\text{SnCl}$        |                                      | 67                       |
| 2     | <b>2</b>         | PhSSPh                          |                                      | 52                       |
| 3     | <b>2</b>         | TosCN                           |                                      | 67                       |
| 4     | <b>2</b>         | PhCHO                           |                                      | 90 <sup>[b]</sup>        |
| 5     | <b>2</b>         | allyl bromide                   |                                      | 75                       |
| 6     | <b>2</b>         | ethyl (2-bromomethyl)acrylate   |                                      | 81                       |
| 7     | <b>2</b>         | PhCOCl                          |                                      | 73                       |
| 8     | <b>2</b>         | 4-iodobenzoic acid methyl ester |                                      | 92                       |
| 9     | <b>5a</b>        | $\text{I}_2$                    |                                      | 85                       |
| 10    | <b>5a</b>        | allyl bromide                   |                                      | 64                       |
| 11    | <b>5a</b>        | PhCHO                           |                                      | 60 <sup>[c]</sup>        |
| 12    | <b>5a</b>        | $\text{Ph}_2\text{CO}$          |                                      | 61                       |
| 13    | <b>5a</b>        | $\text{C}_5\text{H}_8\text{O}$  |                                      | 61                       |
| 14    | <b>5b</b>        | $(\text{BrCl}_2\text{C})_2$     |                                      | 80                       |

[a] Yield of analytically pure isolated product. [b] d.r. = 65:35. [c] d.r. = 92:8.

In the case of the reaction with benzaldehyde, a spontaneous lactonization occurs to give the lactone **3d** as a separable mixture of two diastereoisomers in the ratio of 65:35 (entry 4 of Table 1). In the presence of  $\text{CuCN} \cdot 2\text{LiCl}$ ,<sup>[11]</sup> a smooth reaction proceeds with allyl bromide and ethyl (2-bromomethyl)acrylate<sup>[12]</sup> or benzoyl chloride (entries 5–7). A fast Negishi cross-coupling reaction<sup>[13]</sup> takes place after transmetalation to the corresponding zinc reagent with  $\text{ZnBr}_2$ . An efficient cross-coupling takes place in the presence of bis-dibenzylidenepalladium(0)<sup>[14]</sup> and tris-*o*-furylphosphane<sup>[15]</sup> to give the diester **3h** in 92% yield (25 °C, 6 h, entry 8). Since magnesium carbenoids are an important class of organometallic reagents,<sup>[16]</sup> we have examined the formation of carbenoids<sup>[17]</sup> bearing an ester group. The dibromocyclopropanecarboxylic acid ethyl ester **4a**<sup>[18]</sup> was treated with *i*PrMgCl (1.1 equiv) in THF which resulted in the formation of a 65:35 mixture of diastereomeric carbenoids as indicated by quenching experiments with electrophiles (Scheme 2). The major diastereoisomer was the Grignard reagent **5a**. This ratio of diastereomers did not significantly change with time. However, a completely stereoselective exchange was observed on performing the Br–Mg exchange in diethyl ether (–50 °C, 10 min). This reaction resulted in the formation of the *cis*-magnesium carbenoid **5a** (d.r. > 99:1) which can be stereoselectively trapped by several electrophiles (Scheme 2 and Table 1).



Scheme 2. Synthesis of carbenoids bearing an ester group.

Thus, the reaction of the ester-substituted carbenoid **5a** with iodine furnishes stereoselectively the iodobromocyclopropane **6a** in 85% yield (entry 9). Similarly, the quenching of **6a** with allyl bromide furnishes the expected allylated product **6b** in 64% yield. The reaction of **5a** with various aldehydes or ketones proceeds readily and leads to lactones **6c–e** in 60–61% yield. The reaction with benzaldehyde was highly diastereoselective (d.r. = 92:8) to give **6c** (major isomer depicted in entry 11; its structure has been proven by X-ray analysis<sup>[19]</sup>) in 60% yield. Interestingly, the reaction of carbenoid **5b** generated by the reaction of *i*PrMgCl with the diiodocyclopropanecarboxylic acid ethyl ester **4b**<sup>[20]</sup> in diethyl ether at –50 °C is also highly diastereoselective. The isomeric iodobromocyclopropane derivative **7a** is formed in 80% yield (compare entries 9 and 14) after quenching carbenoid **5b** with 1,2-dibromotetrachloroethane.

In summary, we have reported the stereoselective preparation of functionalized cyclopropylmagnesium derivatives including carbenoids. Under our reaction conditions they are configurationally stable. Applications of these versatile cyclopropylmagnesium reagents and extensions of the preparation of other functionalized alkylmagnesium reagents are currently underway.

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# Self-Assembled, Deterministic Carbon Nanotube Wiring Networks\*\*

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One promise of molecular electronics is that it is potentially amenable to a “bottom-up”, self-assembly-based manufacturing approach. This would provide an interesting alternative for circuit fabrication when devices are scaled to a few tens of nanometers in size and smaller.<sup>[1]</sup> However, major challenges exist in developing architectures suitable to bottom-up fabrication, as well as in devising the circuit fabrication techniques themselves. For example, self-assembly leads most readily to periodic structures,<sup>[2]</sup> and, while the starting materials for such approaches may be highly purified, the assembly steps themselves are unlikely to be perfect. Furthermore, various structural parameters of a circuit that are obtained through lithographic patterning, such as the length, diameter, orientation, and separation (pitch) of the wires, can be substantially more difficult to control by using chemical assembly. Finally, nanowires with the most desirable electrical characteristics, such as single-walled carbon nanotubes (SWNTs), do not necessarily have the chemical properties required for controlled self-assembly.

Four years ago, one of us reported on the relevance of the crossbar circuit for molecular electronics.<sup>[3]</sup> From the perspective of bottom-up assembly, the crossbar is attractive because it is simple, ordered, and defect-tolerant, and it may be utilized for both memory and logic. Here we present a room-temperature, “minimal-lithography” technique for chemically assembling small deterministic crossbars of SWNT ropes. The length of the SWNT ropes is varied from 1 to 20  $\mu\text{m}$  by a solution-phase, chemically controlled aggregation of much shorter ( $\approx 0.5 \mu\text{m}$ ) SWNTs. The orientation and spatial positioning of the SWNTs are induced by an alternating current (AC) electric field. The pitch of the nanotubes within the crossbar is controlled between 100 nm and 2  $\mu\text{m}$ , essentially as a result of the chemical control of the screened Coulombic interactions between the (electrically charged) SWNTs. The electrical charge on the SWNTs is qualitatively

determined by solvent–SWNT interactions. Consequently, all of the critical structural parameters of the crossbars were controlled without lithographic assistance. Low-resolution patterning of the electrodes that generate the AC field was the only lithographic step required. We also report on a theory of the crossbar fabrication, which identifies the important chemical variables for manipulating this self-assembly process. Transport measurements through crossbar assemblies are reported as a consistency check against literature measurements for randomly assembled crossed-SWNT structures.

The excellent conductivity properties of SWNTs make them ideal wiring candidates for molecular-scale circuitry. Dai’s group has developed wafer-based growth procedures that can generate aligned SWNTs.<sup>[4]</sup> However, this technique requires lithographic definition of SWNT nucleation sites, as well as high-temperature processing—neither of which is compatible with molecular-based nanoscale architectures. Lieber’s group has recently reported on a nanowire crossbar fabrication approach that employs microfluidics to align semiconductor nanowires within lithographically defined channels, coupled with deposition onto a chemically patterned surface.<sup>[5]</sup> That approach worked under ambient conditions, and certain parameters, such as nanowire length and diameter, were chemically controlled. However, lithographic definition of some of the critical aspects of the crossbar, such as nanowire pitch and orientation, was required. SWNTs are flexible, have limited solubility, and techniques to control properties such as nanotube length and aggregation have not been well developed. Consequently, most SWNT devices to date have relied on effectively random single-device assembly events, such as the fortuitous crossing of two tubes to produce a single junction.

The controlled aggregation of SWNTs to form ropes, without precipitating the nanotubes, turned out to be critical for ultimately controlling our crossbar structures. Solubilization of SWNTs typically requires the use of surfactants<sup>[6]</sup> or polymer wrapping.<sup>[7]</sup> However, we have been able to disperse HipCO tubes (HipCO = high pressure carbon monoxide) in *ortho*-dichlorobenzene (ODCB) in relatively high concentrations ( $\approx 0.01\%$  by weight) with minimal sonication times ( $\approx 10 \text{ min}$ ). SWNTs produced by the recently developed HipCO (high pressure carbon monoxide) process<sup>[8]</sup> tend to have smaller diameters than SWNTs produced by laser ablation. Atomic force microscopy (AFM) characterization confirms that the dispersed tubes are isolated single strands and/or small ropes, with diameters ranging from 0.8 to 1.3 nm, and lengths from 0.1 to 1.5  $\mu\text{m}$ , with the majority of the tubes being shorter than 0.5  $\mu\text{m}$ . Electroplating experiments revealed that the SWNTs in ODCB are positively charged—a result that we attribute to the large electron affinity of ODCB. By contrast, when SWNTs are suspended using certain nonionic surfactants,<sup>[9]</sup> colloids of negatively charged SWNTs are produced. We achieved controllable aggregation of the SWNTs by diluting a SWNT/ODCB solution with  $\text{CHCl}_3$ . A typical solution is prepared by diluting 1.5 mL of a SWNT/ODCB solution ( $10^{-4}\%$  of SWNT by weight) in 250 mL of  $\text{CHCl}_3$  while sonicating. Such a solution led to SWNT ropes of diameters between 6 and 20 nm and lengths ranging from 1 to

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20  $\mu\text{m}$ , with longer ropes having larger diameters. A lower weight percent of SWNTs led to shorter ropes, while a higher weight percent led to longer ropes. Electroplating experiments indicated that the SWNTs retained their charge after addition of  $\text{CHCl}_3$ .  $\text{CHCl}_3$  and ODCB have similar dielectric constants. Other solvents that were co-miscible with ODCB but that were a poor dielectric match, such as hexane, caused complete precipitation of the SWNTs.

Electric field assisted deposition and orientation of the nanowires<sup>[10, 11]</sup> was accomplished by patterning two parallel electrodes with a 10  $\mu\text{m}$  gap onto a silicon wafer coated with 0.5  $\mu\text{m}$   $\text{SiO}_2$ .<sup>[12]</sup> This device was immersed in a suspension of SWNTs dispersed in a solution that contained 0.4 mL of ODCB and 100 mL of  $\text{CHCl}_3$ . An AC field was generated by applying a 20  $\text{V}_{\text{p-p}}$  AC voltage at 4 MHz for a period of 4 to 15 minutes while the solution was stirred. After deposition, the electrode was chemically etched away, and a new electrode set was deposited perpendicular to the first set. Then, the SWNT deposition was repeated. Previous authors have demonstrated that various nanowires, including SWNTs, when deposited onto a surface, will withstand simple device processing steps.<sup>[13a-c]</sup> We also found this to be the case.<sup>[12]</sup> The electrical character of the assembled crossbars was tested by using electron beam lithography to pattern electrode connections onto several of the SWNTs in a given crossbar.<sup>[13]</sup>

Three SWNT crossbars of varying structural characteristics are shown in Figure 1. A key result of this work is that the pitch of the crossbar was controllable and correlated with the length of the SWNT ropes. As the width of the length distribution of the SWNT ropes increased, the fluctuations in crossbar pitch also increased (Figure 2).

We have developed a model of this assembly process to understand the various chemical and physical parameters that can be used to control crossbar formation. The fact that a characteristic length scale (the pitch) arises during the crossbar fabrication process is the result of inter-SWNT rope repulsive interactions that are strongly screened by the solvent and the ODCB counterions, as suggested by the experimental observation that the solvated ropes are positively charged. The constrained geometry of the electrodes also plays an important role. Because of the field-generated alignment force, the deposition of the ropes is effectively confined to a single dimension and a local area—that is, perpendicular to the electrode stripes and within the area between the two electrodes.<sup>[14]</sup> The first ropes to arrive deposit parallel to each other (aligned to the field) at random positions on the electrode and, once deposited, they remain in their positions due to large van der Waals interactions with the substrate. However, as the density of deposited ropes increases, the electric field in their vicinity is modified by their presence. An incoming rope will then fall at the point of lowest repulsion from its neighboring ropes; for example, equidistant between ropes of equal length. During this process, a point will be reached at which tube repulsion will balance the driving force to deposition, resulting in a critical inter-rope distance or pitch ( $p$ ).

This critical condition may be understood from the local energetics of the problem: the screened interaction (repulsive) energy of the incoming rope with the already deposited

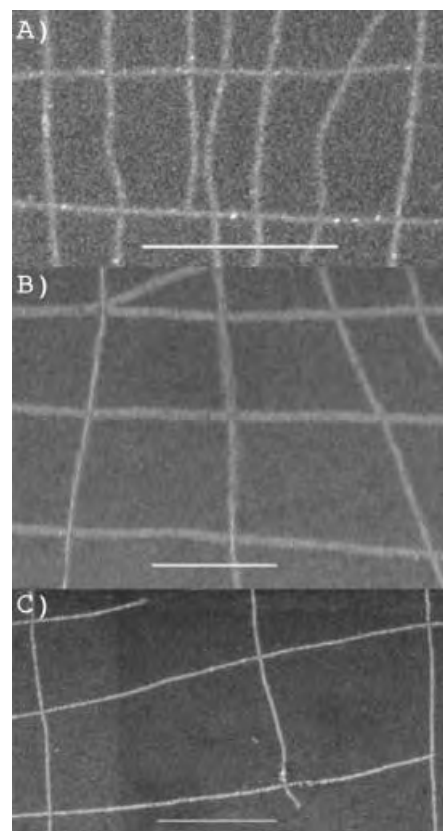


Figure 1. Scanning electron micrographs of SWNT crossbars with varying pitch. Scale bars are 500 nm for a) and b), and 1  $\mu\text{m}$  for c). The diameter of the ropes is not well measured with this technique, but can be measured with force microscopy. The shortest (500 nm) wires are characterized by diameters of 1–2 nm, while the longest (20  $\mu\text{m}$ ) wires possess diameters ranging from 10 to 15 nm. SWNT rope lengths [ $\mu\text{m}$ ]: a)  $3.7 \pm 0.3$  &  $1.2 \pm 0.33$ ; b)  $2.8 \pm 0.53$ ; c)  $3.8 \pm 1.2$ .

ropes is balanced against its Coulomb and polarization energies under the external field. In fact, the Coulomb energy is the dominant contribution in the experimental conditions considered here. We believe that a thin charged rod will capture the main features of the electrostatic processes of the SWNTs involved. Although their transport properties ensue from their quantum nature, nanotubes behave as classical objects in many other respects. In particular, *ab initio* calculations<sup>[15]</sup> have shown that the screening of applied electric fields by nanotubes is remarkably similar to that of cylindrical conductors with equivalent aspect ratio.<sup>[16]</sup>

To obtain the electrostatic potential of the deposited tubes in the presence of surrounding counterions (ODCB) in a solvent with a dielectric constant  $\epsilon$  ( $\text{CHCl}_3$ ), we use the linearized Poisson-Boltzmann (PB) equation.<sup>[12]</sup> The key aspect of the solvation process is the appearance of a characteristic screening length  $1/\kappa$  given by equation (1),

$$\kappa^2 = \frac{4\pi(qe)^2}{\epsilon k_B T} \rho_c \quad (1)$$

where  $e$  is the fundamental unit of charge,  $qe$  the counterion charge,  $T$  the temperature,  $k_B$  the Boltzmann constant, and  $\rho_c$  the ionic ODCB density. The ropes have a large aspect ratio, so they can be characterized by  $\lambda$ , which is their line charge density per unit length. Thus,  $\rho_c$  may be estimated from the

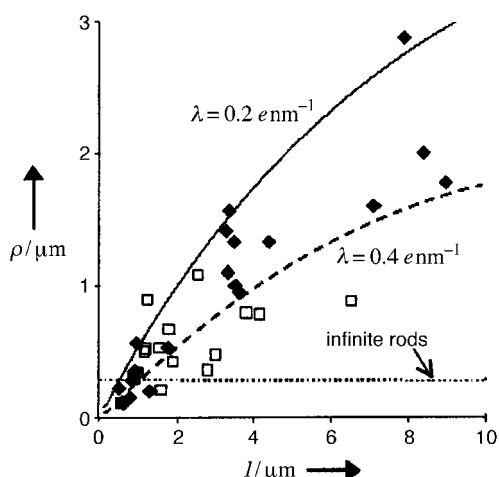


Figure 2. The pitch  $[p/\mu\text{m}]$  versus the rope length  $[l/\mu\text{m}]$ , calculated for two linear charge densities  $[\lambda/e\text{nm}^{-1}]$  and for  $\rho_t = 4 \times 10^9$  tubes per mL in a  $\text{HCCl}_3$  solution with ODCB counterions. Experimental data, plotted as black diamonds and open squares, represents crossbars formed from tubes that were characterized by similar lengths to within 25% and 50%, respectively. In spite of their large aspect ratios, the ropes interact with each other more like finite charges rather than infinite rods, at regimes determined by  $\kappa l \sim 1$ . This condition holds except for the shortest ropes ( $l < 2 \mu\text{m}$ ), in which case the screening lengths overlap strongly and so the approximations used in the model are no longer valid. For comparison, the solution obtained from infinite rods is also plotted. For that case, there is no length dependence, but the limiting behaviors show that it is not the absolute length that makes a rod behave as “infinite” but rather its values  $\kappa l$  and  $\kappa r$ . Note that the charge density  $\lambda$  does not necessarily correspond to its experimental counterpart, as the theory requires  $\lambda$  to be suitably renormalized.

condition of overall charge neutrality  $q\rho_c = \lambda \langle l \rangle \rho_t$ , where  $\rho_t$  is the number density of tubes in solution<sup>[12]</sup> and  $\langle l \rangle$  is the average tube length.

The screening length  $1/\kappa$  not only determines the attenuation of the inter-rope repulsion, but, significantly, it establishes the interplay of length scales involved in this problem. In particular, it discriminates among the different asymptotic regimes of the potential. At one extreme,<sup>[17]</sup> rods of length  $l$  separated by distances  $r \ll l$  with  $\kappa l \gg 1$  behave as infinite rods. Their potential can be described by the Bessel function of order zero. At the other extreme,<sup>[18]</sup> rods with length  $l \ll r$  and  $\kappa l \sim 1$  behave as equivalent point charges of magnitude  $\lambda l$ , as described by the Yukawa potential. The experimental conditions ( $\kappa \sim 1 \mu\text{m}^{-1}$ ,  $l \sim 1 \mu\text{m}$ , so  $\kappa l \sim 1$ ,  $r \sim l$ ) fall in the intermediate regime but closer to the point charge regime. Hence, we use the more appropriate Yukawa potential (per unit length)  $\phi = \frac{\lambda \exp(-\kappa r)}{\epsilon r}$  to obtain the energy. This yields the critical relationship of pitch ( $p$ ) with SWNT rope length ( $l$ ) [Eq. (2)], where  $E$  is the electric field and  $\alpha = \alpha(l)$  is the polarizability; we have assumed ropes of equal length.

$$U(p/2) = \left( \frac{2\lambda l \exp(-\kappa p/2)}{p/2} - V_{\text{ext}} \right) \frac{\lambda l}{\epsilon} - \frac{\alpha E^2}{2} = 0 \quad (2)$$

We also assumed ODCB counterions with charge  $-e$ , although there is no qualitative difference for smaller values. In Figure 2 we compare some numerical solutions of this equation to the experimental data. Consistent with our assumptions, the agreement is better when the deposited

SWNT ropes are of nearly equal length. The model also underscores the importance of correctly describing the solvation process: both the screened and bare infinite rod limits fail to reproduce the experiments. These results imply that experimental control over the SWNT length is a critical chemical handle for manipulating crossbar formation: longer ropes with higher polarizability should lead to a decrease in the pitch. This should be complemented by an optimization of the interplay between polarizability and the properties of the applied voltage.<sup>[14]</sup>

These crossbars are not meant to serve as models for interrogating transport physics through nanotubes. Nevertheless, simple transport experiments can address whether the junctions actually conduct, and whether or not the assembly technique, which bears some similarities to electrophoretic separation approaches,<sup>[14]</sup> might be selective for tube type, although it is unlikely that such selectivity would be important at frequencies as low as 4 MHz. Using standard e-beam lithography procedures, we wired up and interrogated the electrical character of a number of aligned SWNT ropes and found that the ropes were, in fact, a statistical mix of metals and semiconductors.<sup>[12]</sup> The current–voltage characteristics of a single SWNT rope, and for a crossed junction containing that rope, are presented in Figure 3. This particular junction is

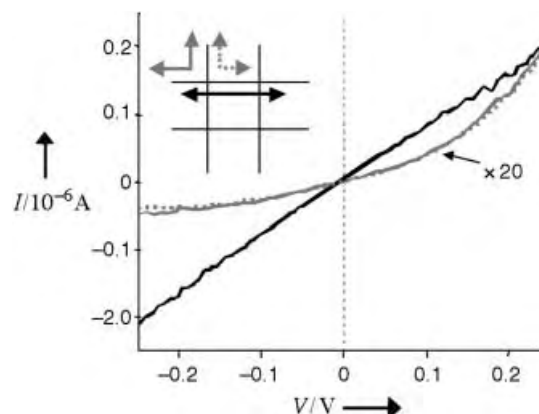


Figure 3. Transport through a single wire (black curve) and through a crossed junction (dotted curve) of a nine-junction nanotube crossbar structure.

dioidic, perhaps resulting from a metallic rope crossing a semiconducting rope.<sup>[19]</sup> Both dioidic and ohmic responses were observed for other junctions. These results indicate that the junctions are reasonably conducting, although the current through our devices is relatively low,<sup>[12, 19, 20]</sup> perhaps because of contact resistance. The devices could be annealed at elevated temperatures, which resulted in higher conductivity. However, for our particular applications, thermal annealing must be balanced against the requirements for incorporating molecules into the nanotube junctions, and so we report only unannealed devices here.

Our results indicate that it is possible to fabricate deterministic wiring networks from SWNTs by using chemical self-assembly. While this process is currently limited to the fabrication of relatively small ( $4 \times 4$  and less) crossbars, our

simple model indicates that the optimization of several experimental handles may lead to the assembly of large-scale structures. For example, maximizing the length and mono-dispersity of the SWNT ropes, as well as controlling dielectric screening and SWNT charge density, are all identified as key handles for improving this process. Furthermore, the frequency of the orienting AC field represents a variable that has not yet been optimized. We found little frequency dependence to this process between  $10^4$  Hz and  $10^6$  Hz. This is likely because the intertube Coulomb repulsions are dominant in this regime. However, at much higher frequencies, our calculations suggest that the polarizability of the tubes should become important, at which point the circuit pitch may decrease as it approaches the limit for infinite rods (Figure 2). We are currently designing experiments at  $>10^9$  Hz deposition frequencies to explore this effect. We remark that none of these experimental handles to circuit fabrication require the use of lithographic techniques. Thus, relatively inexpensive routes toward fabricating designed circuits with characteristic dimensions on the order of a few nanometers may be possible.

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## Protein Affinity Labeling Mediated by Genetically Encoded Peptide Tags\*\*

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Kathlynn C. Brown\*

Affinity labeling is a powerful method by which protein residues in the immediate vicinity of a labeled ligand can be identified. Most such experiments employ latently photo-activatable groups such as benzophenones<sup>[1]</sup> or azides<sup>[2]</sup> attached covalently to a ligand of interest. When photolyzed, the resultant intermediate inserts into a carbon–hydrogen bond of the protein which results in the covalent coupling of the molecule of interest with its receptor. These experiments generally have been employed to identify active site residues proximal to the site of ligand or substrate binding.<sup>[3, 4]</sup>

Traditional affinity-labeling techniques have limitations when the ligand of interest is a protein and the goal is to identify the binding partners of that protein. With the exception of small proteins that contain only a single nucleophilic cysteine,<sup>[5]</sup> it is difficult to produce site-specifically labeled proteins by standard conjugation chemistry. An appealing solution to this problem would be to develop a genetically encoded peptide tag capable of binding an affinity-labeling reagent with high specificity. We demonstrate here that the complex of Ni<sup>II</sup> with the tripeptide NH<sub>2</sub>-glycine-

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glycine-histidine ( $\text{NH}_2\text{-GGH}$ ) or the hexahistidine peptide ( $\text{His}_6$ ) can mediate biotinylation of proximal proteins by an oxidatively triggered reaction. This method should be useful for labeling and identifying the binding partners of a given protein.

$\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$  is a stable complex<sup>[6]</sup> that, when activated by a peracid,<sup>[7]</sup> mediates several oxidative reactions<sup>[8–10]</sup> including protein cross-linking, a process that is thought to be initiated by  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{III}}$ -mediated oxidation of tyrosine.<sup>[11, 12]</sup> In analogy with previous work with antibody–horseradish peroxidase conjugates,<sup>[13, 14]</sup> it was anticipated that oxidative activation of the nickel center in the presence of high levels of free biotin-tyramine would lead to the formation of a tyramine radical. Subsequent radical coupling to suitable groups on the surfaces of nearby proteins would mark them with biotin (Scheme 1).

To test this,  $\text{NH}_2\text{-GGH-ecotin}$ ,<sup>[12]</sup> a homodimeric macromolecular serine protease inhibitor, was incubated in the presence of  $\text{Ni}^{\text{II}}$ , the peracid magnesium monoperoxyphthalate (MMPP), and biotin-tyramine. One tenth of the sample was then separated by SDS-PAGE, transferred onto a nitrocellulose membrane, and probed with avidin, which binds biotin tightly and specifically (see Supporting Information for a detailed protocol). Four major biotinylated species were detected which had the mobilities expected of the ecotin monomer, dimer, and two multimers. This indicates that both biotinylation and protein cross-linking<sup>[11, 12, 15–17]</sup> had occurred (Figure 1, lane 1). Biotin-tyramine,  $\text{Ni}^{\text{II}}$ , MMPP, and the  $\text{NH}_2\text{-GGH}$  tag were each required for labeling (Figure 1, lanes 2–5). Quantification of the level of biotinylation revealed that, on average, three to four molecules of biotin-tyramine were coupled to one molecule of ecotin (see Supporting Information).

After we had demonstrated that the  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$  complex can support the basic reaction, we investigated the more interesting possibility of labeling a binding partner of the tagged protein. Ecotin is known to inhibit trypsin with a  $K_i$  in the nanomolar range.<sup>[18]</sup> When the GGH-ecotin labeling experiment was repeated in the presence of trypsin, the protease was also biotinylated (Figure 2, lane 2). Biotinylated

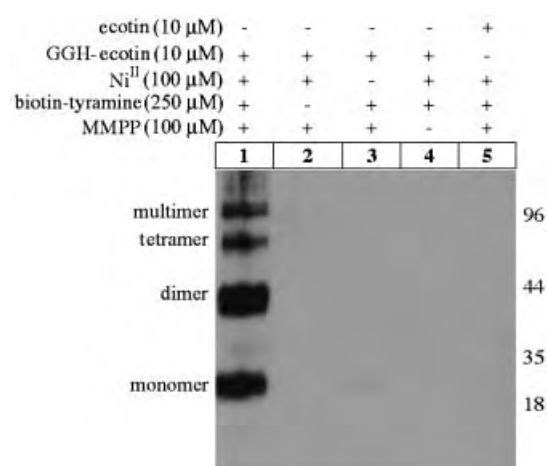


Figure 1. The  $\text{NH}_2\text{-GGH}$  tag supports the self-labeling of a tagged protein in the presence of  $\text{Ni}^{\text{II}}$ , biotin-tyramine, and MMPP (lane 1). The GGH tag,  $\text{Ni}^{\text{II}}$ , biotin-tyramine, and MMPP are all required for oxidative labeling (lanes 2–5). One tenth of the sample was separated by SDS-PAGE, transferred to nitrocellulose, and probed with avidin-HRP.

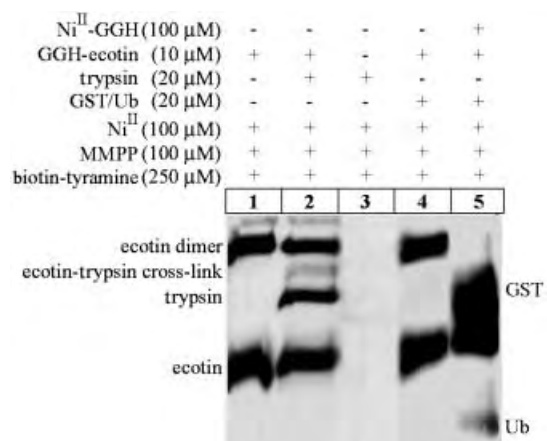
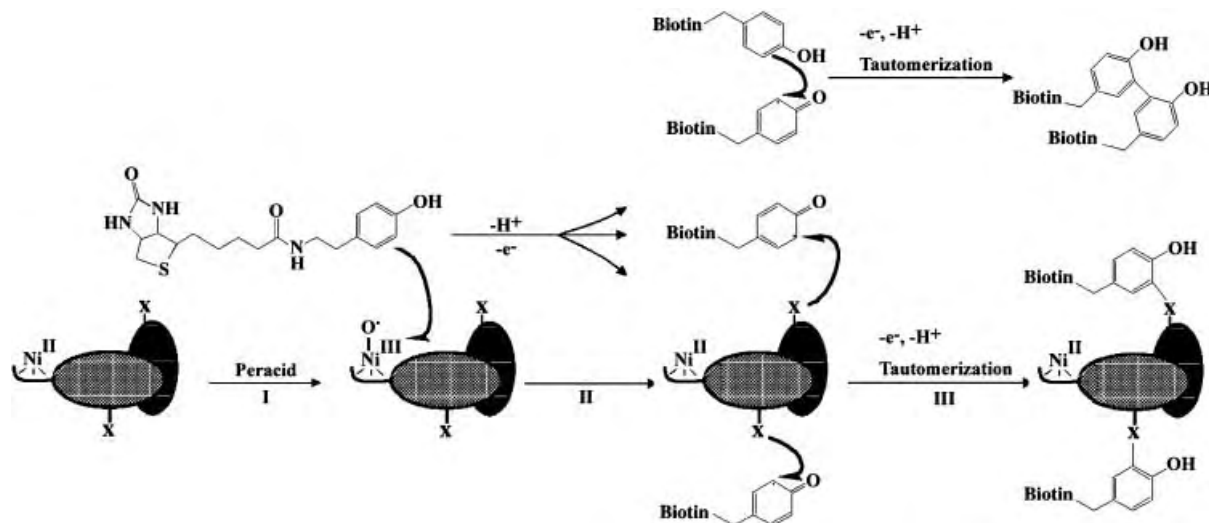


Figure 2. The  $\text{NH}_2\text{-GGH}$  tag supports the localized labeling of a tagged protein's binding partner but not to noninteracting proteins. One tenth of the sample was separated by SDS-PAGE, transferred to nitrocellulose, and probed with avidin-HRP.



Scheme 1. Proposed mechanism for biotinylation.

trypsin was not detected in the absence of GGH-ecotin, which rules out the possibility of self-labeling as a result of spurious metal-binding sites on the protease (Figure 2, lane 3).

For this methodology to be useful for probing protein–protein interactions, labeling must be limited to proteins that are in close proximity to the  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$  tag. To probe this point, glutathione *S*-transferase (GST) and ubiquitin (Ub) were included in the reaction along with GGH-ecotin. Only GGH-ecotin was labeled (Figure 2, lane 4), which indicates that the affinity-labeling chemistry is localized. However, when exogenous  $\text{NH}_2\text{-GGH-COOH}\cdot\text{Ni}^{\text{II}}$  was added to the solution, all three proteins were labeled (Figure 2, lane 5). This observation confirmed that the lack of biotinylation of GST and Ub did not result from their lack of suitable reactive groups on their surfaces.

To probe the issue of nonspecific labeling in a more demanding venue, biotinylation experiments were conducted with phage fd-tet<sup>[19]</sup> genetically modified to display GGH at the N-terminus of gpIII. Three to five copies of gpIII are displayed at one end of the filamentous phage particle, whereas 2800 copies of gpVIII constitute most of the rest of the phage surface.<sup>[20]</sup> Incubation of a GGH-gpIII fd-tet phage strain with  $\text{Ni}^{\text{II}}$ , biotin-tyramine, and MMPP resulted in the exclusive labeling of gpIII (Figure 3, lane 1). However, the incubation of the phage with exogenous  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$ , MMPP, and biotin-tyramine resulted in the biotinylation of both coat proteins (Figure 3, lane 2), which confirms that gpVIII can be labeled, albeit less efficiently,<sup>[21]</sup> by this chemistry.

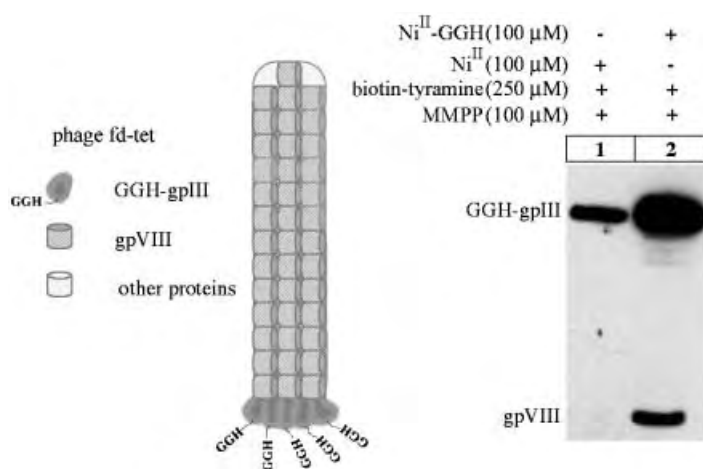


Figure 3. Affinity labeling of the phage fd-tet outer coat protein  $\text{NH}_2\text{-GGHgpIII}$ .  $5 \times 10^{11}$  phage particles were treated with biotinylation reagents. One tenth of the sample was separated by SDS-PAGE, transferred to nitrocellulose, and probed with avidin-HRP.

The lack of detectable intramolecular labeling of gpVIII in the above experiment, despite its abundance, and the inability of  $\text{NH}_2\text{-GGH-ecotin}$  to label GST and Ub argue that  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$ -mediated biotinylation has a sufficiently short “range” that proteins not associated with the tagged protein are not biotinylated to a significant degree. This is likely a result of the dimerization of biotin-tyramine through a phenolic coupling mechanism if the radical form escapes into bulk solution (Scheme 1).

A limitation of the  $\text{NH}_2\text{-GGH}$  tag is that it binds  $\text{Ni}^{\text{II}}$  only when present at the N-terminus of a protein. This is because the terminal main chain amino group is directly involved in metal complexation.<sup>[22]</sup> While the GGH tag can be revealed on the N-terminus by site-specific proteolysis,<sup>[23]</sup> the utility of affinity labeling could be expanded if other more versatile peptide tags were able to mediate the biotinylation chemistry. The  $\text{His}_6$  tag also binds  $\text{Ni}^{\text{II}}$ , albeit not as well as  $\text{NH}_2\text{-GGH}$ , and can do so when placed anywhere in a polypeptide, so long as protein function is not compromised by the insertion. Furthermore,  $\text{His}_6\cdot\text{Ni}^{\text{II}}$  complex, like  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$ , supports oxidative protein cross-linking,<sup>[16, 17]</sup> which suggests that it might be active in biotinylation as well.

A  $\text{His}_6$ -tagged derivative of the dimeric yeast Gal80 transcriptional repressor, where the tag represents residues 5–10 of the fusion protein, was expressed and purified.<sup>[24]</sup> A GST fusion protein with the C-terminal activation domain of Gal4 (GST-AD), Gal80’s native binding partner,<sup>[25]</sup> was also isolated. Under the same conditions used for  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$ -mediated reactions, the  $\text{His}_6$  tag also supports the localized oxidative biotinylation of a tagged protein and its target. As shown in lane 1 of Figure 4, both the monomeric

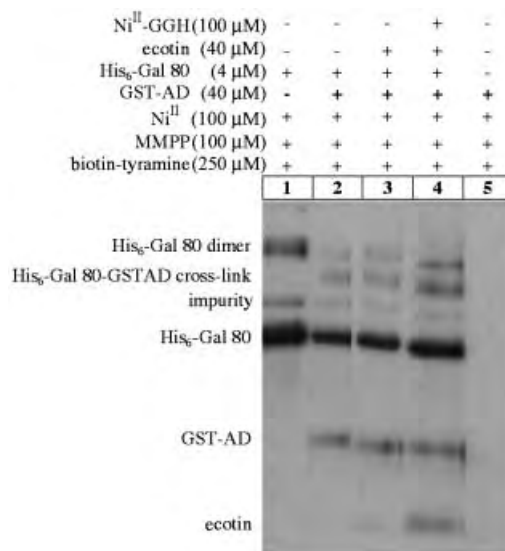


Figure 4. The  $\text{His}_6$  tag mediates localized affinity labeling. Reactions were performed under the same conditions used for  $\text{NH}_2\text{-GGH}\cdot\text{Ni}^{\text{II}}$ -mediated reactions. One tenth of the sample was separated by SDS-PAGE, transferred to nitrocellulose, and probed with avidin-HRP.

and dimeric cross-linked products of  $\text{His}_6\text{-Gal80}$  were biotinylated in the presence of  $\text{Ni}^{\text{II}}$ , MMPP, and biotin-tyramine. More importantly, GST-AD was also biotinylated when it was included in the reaction (Figure 4, lane 2). A new species with the molecular weight of a GST-AD-Gal80 cross-linked product was also biotinylated. However, only trace amounts of untagged ecotin were labeled when it was included (Figure 4, lane 3). This provides evidence that the  $\text{His}_6$  tag mediates localized affinity labeling. A control reaction with exogenous  $\text{NH}_2\text{-GGH-COOH}\cdot\text{Ni}^{\text{II}}$  complexes again resulted in the biotinylation of all of the proteins present (Figure 4, lane 4). Likewise, the failure to detect biotinylated GST-AD

products in the absence of His<sub>6</sub>-Gal80 ruled out the possibility of GST-AD self-labeling (Figure 4, lane 5). Biotinylation was not detected when the His<sub>6</sub> tag was removed from Gal80, or when Ni<sup>II</sup> MMPP or biotin-tyramine were omitted from the reaction (data not shown).

The detailed mechanism of the affinity-labeling reaction remains to be elucidated. However, it most likely proceeds through initial oxidation of the Ni<sup>II</sup>-peptide complex by MMPP to form a high valent Ni<sup>III</sup>-oxo species,<sup>[7]</sup> which subsequently abstracts an electron from the phenol group of a biotin-tyramine. The radical formed following loss of a proton from the radical cation could then couple to tyrosine or other suitably reactive amino acids on a tagged protein and any other proteins in the immediate vicinity. It is speculated that protein biotinylation is localized to the immediate region of the metal-binding tag by efficient quenching of the radical by excess biotin-tyramine in solution through phenolic coupling (Scheme 1).

In summary, we have demonstrated that two simple Ni<sup>II</sup>-peptide complexes can mediate localized affinity-biotinylation reactions. This is a potentially useful tool for studying protein-protein interactions, particularly in the context of large complexes where it is difficult or impossible to label a particular protein uniquely with an azide- or benzophenone-containing reagent by using standard methods. Experiments in which this system is applied to such complex systems are underway.

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## Expanding Divalent Organolanthanide Chemistry: The First Organothulium(II) Complex and the In Situ Organodysprosium(II) Reduction of Dinitrogen\*\*

William J. Evans,\* Nathan T. Allen, and Joseph W. Ziller

Although historically the organometallic chemistry of the divalent lanthanides has involved just three ions, Eu<sup>2+</sup>, Yb<sup>2+</sup>, and Sm<sup>2+</sup>, these elements have provided an extensive series of unusual structures and reactions.<sup>[1]</sup> Recently, however, opportunities have arisen to expand divalent lanthanide chemistry to other metals in the series.<sup>[2]</sup> The isolation of the first molecular complex of divalent thulium, [TmI<sub>2</sub>(dme)<sub>3</sub>] (dme = dimethoxyethane) in 1997,<sup>[2a]</sup> provided an analogue of the commonly used [SmI<sub>2</sub>(thf)<sub>x</sub>],<sup>[3]</sup> a precursor to organosamarium(II) complexes such as [(C<sub>5</sub>Me<sub>5</sub>)<sub>2</sub>Sm(thf)<sub>x</sub>].<sup>[4]</sup> Ionic metathesis reactions with [TmI<sub>2</sub>(dme)<sub>3</sub>] could provide a direct route to divalent organothulium complexes, but the high reactivity of Tm<sup>2+</sup> made this challenging (reduction potentials versus NHE: Tm<sup>2+</sup> – 2.3 V; Sm<sup>2+</sup> – 1.5 V).<sup>[5]</sup> In fact, since 1997 only one other Tm<sup>2+</sup> derivative has been reported in the literature.<sup>[6]</sup>

The discovery of TmI<sub>2</sub> as an in situ organic reagent<sup>[7]</sup> initiated a study of the organometallic chemistry of Tm<sup>2+</sup> showing why organothulium(II) complexes are so difficult to isolate. Nitrogen is not inert to these species; they react to form complexes such as [[[C<sub>5</sub>H<sub>3</sub>(SiMe<sub>3</sub>)<sub>2</sub>]<sub>2</sub>Tm]<sub>2</sub>N<sub>2</sub>], [[[C<sub>5</sub>Me<sub>5</sub>]<sub>2</sub>Tm]<sub>2</sub>N<sub>2</sub>], and [[[C<sub>5</sub>H<sub>4</sub>SiMe<sub>3</sub>]<sub>2</sub>Tm(thf)<sub>2</sub>N<sub>2</sub>]].<sup>[8]</sup> Initial attempts to isolate organothulium(II) complexes under argon led to decomposition of the diethyl ether solvent to make ethoxide and oxide products.<sup>[8]</sup> Herein, we report that by choosing the proper combination of solvents, ligand, and reaction conditions, the first organometallic complex of Tm<sup>2+</sup> has been isolated and structurally characterized.

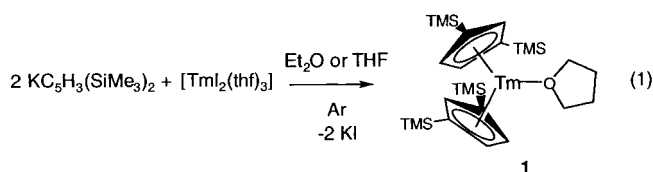
Although the reaction of KC<sub>5</sub>Me<sub>5</sub> with [TmI<sub>2</sub>(thf)<sub>3</sub>] in Et<sub>2</sub>O under argon leads to diethyl ether decomposition, the use of

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$\text{KC}_5\text{H}_3(\text{SiMe}_3)_2(\text{KCp}'')$ <sup>[9]</sup> in either diethyl ether or THF allows the isolation of the organometallic thulium(II) complex  $[\text{Cp}_2''\text{Tm}(\text{thf})]$  (**1**) in 90 % yield [Eq. (1);  $\text{TMS} = \text{SiMe}_3$ ].



The purple solution of **1** in diethyl ether under argon is stable for several hours at 25 °C and for several weeks at –30 °C. While the THF of solvation aids in the isolation of single crystals, the dark green solutions of **1** in THF have lower stability; dilute solutions transform to the yellow color of  $\text{Tm}^{3+}$  complexes over a period of 30 min at 25 °C. Addition of THF to a purple ethereal solution of **1** initiates a color change to dark green. Such intense colors and color changes due to the addition of donor ligands are typical of divalent lanthanides.<sup>[1e, 10]</sup>

Complex **1** can be isolated as purple single crystals at –30 °C (Figure 1), and is isomorphous with the ytterbium analogue  $[\text{Cp}_2''\text{Yb}(\text{thf})]$  reported in 1996.<sup>[11]</sup> This is not unusual

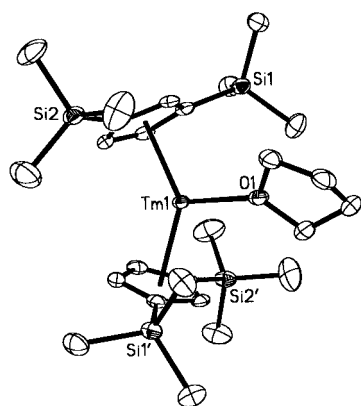


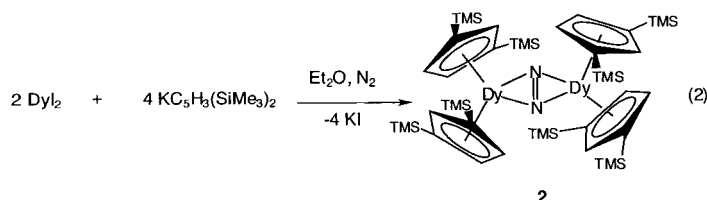
Figure 1. Molecular structure of **1** (with thermal ellipsoids drawn at the 50% probability level).

considering the similarity of the ionic radii;  $\text{Tm}^{2+}$  and  $\text{Yb}^{2+}$  differ by about 0.01 Å.<sup>[12]</sup> The  $\text{Tm}^{2+}$  ion in **1** lies on a crystallographic twofold axis. The (Cp'' ring centroid)–Tm–(Cp'' ring centroid) angle is 135.1° compared to 136° in the Yb analogue. The Tm–(Cp'' ring centroid) and Tm–O(THF) distances of 2.394 and 2.365(5) Å, respectively, are also very close to those for Yb, 2.39 and 2.34(1) Å, respectively.

Since divalent thulium is isoelectronic with  $\text{Yb}^{3+}$  ( $\mu = 4.5$ ) and  $^1\text{H}$  NMR spectra have been successfully obtained for organometallic  $\text{Yb}^{3+}$  complexes,<sup>[13]</sup> the NMR spectra of **1** were examined. Spectra were observed, but since small amounts of  $\text{Tm}^{3+}$  can have a drastic effect on the observed shifts, and the spectra degrade with time as  $\text{Tm}^{2+}$  ( $\mu = 4.6$ ) converts to  $\text{Tm}^{3+}$  ( $\mu = 7.6$ ), specific assignments should not be made until data on related complexes are obtained. The  $^1\text{H}$  NMR spectrum contained resonance signals with half height peak widths of 50–100 Hz in the range  $\delta = -74$  to 15. The  $^{13}\text{C}$  NMR

spectrum shows a peak at  $\delta = -4$ , which is assigned to a methyl resonance signal on the basis of a DEPT experiment.

In efforts to expand divalent organolanthanide chemistry to the even more reducing  $\text{Dy}^{2+}$  (–2.5 V versus NHE), in situ organometallic chemistry with  $\text{DyI}_2$ <sup>[2f, 14]</sup> was examined. Reaction of  $\text{DyI}_2$  with  $\text{KCp}''$  in  $\text{Et}_2\text{O}$  under nitrogen allows isolation of an organodysprosium(II) reduction product, the  $\text{Dy}^{\text{III}}$  dinitrogen complex,  $[[[\text{C}_5\text{H}_3(\text{SiMe}_3)_2]_2\text{Dy}]_2\text{N}_2]$  (**2**) [Eq. (2)].



Although detailed information about the bond lengths could not be obtained due to the quality of the crystals, the structural data showed that the structure of **2** (Figure 2) is the

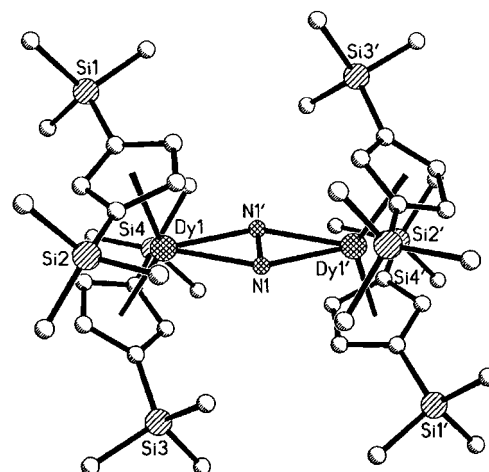


Figure 2. Molecular structure of **2**.

same as that of  $[[[\text{C}_5\text{H}_3(\text{SiMe}_3)_2]_2\text{Tm}]_2\text{N}_2]$ .<sup>[8]</sup> Hence, complex **2** has the same planar  $\text{Ln}_2\text{N}_2$  array as previously observed for the metallocenes  $[[(\text{C}_5\text{Me}_5)_2\text{Ln}]_2\text{N}_2]$  ( $\text{Ln} = \text{Sm}, ^{[15]} \text{Tm}^{[8]}$ ),  $[[[\text{C}_5\text{H}_3(\text{SiMe}_3)_2]_2\text{Tm}]_2\text{N}_2]$ ,<sup>[8]</sup> and  $[[(\text{C}_5\text{H}_4\text{SiMe}_3)_2\text{Tm}(\text{thf})]_2\text{N}_2]$ .<sup>[8]</sup> This once rare planar  $\text{Ln}_2\text{N}_2$  geometry<sup>[15]</sup> has now been found in many lanthanide systems<sup>[2c, 16]</sup> and appears to be a general structural feature for lanthanide–dinitrogen complexes.

The isolation of **1** demonstrates that under the proper conditions with suitable combinations of solvents and ligands, organometallic complexes of  $\text{Tm}^{\text{II}}$  are isolable directly from  $\text{Tm}^{2+}$  precursors. The formation of **2** shows that organodysprosium(II) chemistry is viable in situ, but it should be conducted under an atmosphere more inert than nitrogen. Preliminary studies under argon show  $\text{Dy}^{\text{II}}$  to be highly reactive.

# Experimental Section

**1:** In an argon-filled glovebox, the addition of  $\text{KC}_3\text{H}_3(\text{SiMe}_3)_2$  (175 mg, 0.70 mmol) to an emerald green solution of  $[\text{TmI}_2(\text{thf})_3]$  (200 mg, 0.35 mmol) in THF or diethyl ether (10 mL) caused an immediate color change to dark green, with the concurrent production of white insoluble material. After centrifugation to remove the insoluble material, removal of the solvent under vacuum gave a purple powder (230 mg, 90%). Dissolving the purple solid in  $\text{Et}_2\text{O}$ /hexanes and cooling to  $-30^\circ\text{C}$  provided crystals suitable for X-ray diffraction.  $^1\text{H}$  NMR (500 MHz,  $[\text{D}_8]\text{THF}$ ,  $25^\circ\text{C}$ ):  $\delta = 12$  ( $\Delta\nu_{1/2} = 370$  Hz), 4 ( $\Delta\nu_{1/2} = 45$  Hz),  $-3$  ( $\Delta\nu_{1/2} = 50$  Hz),  $-4$  ( $\Delta\nu_{1/2} = 370$  Hz),  $-74$  ( $\Delta\nu_{1/2} = 50$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $[\text{D}_8]\text{THF}$ ,  $25^\circ\text{C}$ ):  $\delta = -4$  ( $\text{CH}_3^-$ , by DEPT); IR (KBr):  $\tilde{\nu} = 2953, 1768, 1703, 1365, 1359, 1283, 1223, 1207, 1174, 1136, 1114, 1082, 1027\text{ cm}^{-1}$ ;  $\mu_{\text{eff}}$  (298 K) =  $4.6\ \mu_{\text{B}}$ ; elemental analysis (%) calcd for  $\text{C}_{26}\text{H}_{50}\text{Si}_4\text{OTm}$  (659.95): Tm 25.60; found: Tm 25.2. Compound **1** crystallizes in the space group *Pbcn* with  $a = 11.3735(8)$ ,  $b = 13.6274(10)$ ,  $c = 21.2905(16)\text{ \AA}$ ,  $V = 3299.8(4)\text{ \AA}^3$ , and  $\rho_{\text{calcd}} = 1.328\text{ Mg m}^{-3}$  for  $Z = 4$  at  $168(2)\text{ K}$ . At convergence,  $wR2 = 0.0909$  and  $\text{GOF} = 1.231$  for 246 variables refined against 2786 data ( $0.85\text{ \AA}$  resolution). As a comparison for refinement on  $F$ ,  $R1 = 0.0317$  for those 2158 data with  $I > 2.0\sigma(I)$ .

**2:** In a nitrogen-filled glovebox, solvent-free  $\text{DyI}_2^{[2f]}$  (100 mg, 0.24 mmol) was added to a solution of  $\text{KC}_3\text{H}_3(\text{SiMe}_3)_2$  (125 mg, 0.5 mmol) in  $\text{Et}_2\text{O}$  (10 mL). After 2 h at  $-15^\circ\text{C}$ , the solution was centrifuged to remove a white precipitate (KI) leaving a dark orange solution. Addition of hexanes at  $-30^\circ\text{C}$  gave crystals suitable for X-ray analysis (120 mg, 75%). Compound **2** crystallizes in the space group *P1̄* with  $a = 11.4581(9)$ ,  $b = 11.965(1)$ ,  $c = 12.653(1)\text{ \AA}$ ,  $\alpha = 118.1662(11)^\circ$ ,  $\beta = 102.3962(13)^\circ$ ,  $\gamma = 96.1780(13)^\circ$ ,  $V = 1449.134(0.341)\text{ \AA}^3$ . The X-ray data established connectivity, but were not sufficient for detailed bond length analysis.

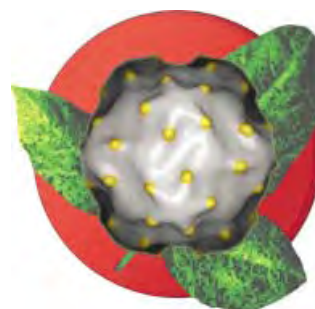
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## COVER PICTURE

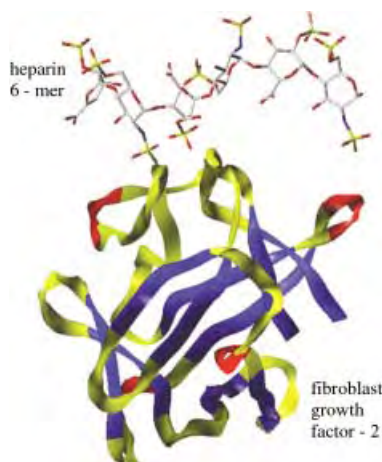
**The cover picture shows** a cowpea plant heavily infected with cowpea mosaic virus (background). A simple isolation procedure provides high yields of pure virus, which can be derivatized selectively by chemical reagents. The particles therefore behave in many respects like prefabricated dendrimers on a nanochemical (30 nm diameter) scale. Their polyvalency is highlighted by the foreground image, showing a cryo-electron microscopy analysis of the virus bearing gold clusters at each of 60 reactive cysteine residues introduced by site-directed mutagenesis. Further details are reported by J. E. Johnson and M. G. Finn and co-workers on p. 459ff.



## REVIEWS

Contents

**Various important physiological and pathophysiological processes** in the human body are thought to be mediated by the interaction of heparin and heparan sulfate with proteins (an example is shown). These interactions have a high degree of specificity in most cases. Thus, understanding their molecular basis is important for the development of highly specific drug candidates.



I. Capila, R. J. Linhardt \* ..... 390–412

Heparin–Protein Interactions

**Keywords:** carbohydrates • coagulation • heparin • medicinal chemistry • molecular recognition

*Angew. Chem.* **2002**, *114*, 426–450

**“Preparing the world for the challenges of the next century”** is one of the goals of Agenda 21, the work program adopted for the 21st century in Rio by 179 countries. One of these challenges is that nine billion people will soon live on the earth and—according to the principles of the Rio Declaration—they all are entitled to a healthy and productive life in harmony with nature. If these principles are to be implemented, then the role of chemistry must also be rethought. This review, which coincides with the World Summit on Sustainable Development 2002 in Johannesburg, indicates new ideas on innovations in chemistry with regard to their ecological, economical, and social dimension.

*Angew. Chem.* **2002**, *114*, 402–425

M. Eissen, J. O. Metzger,\* E. Schmidt,  
U. Schneidewind ..... 414–436

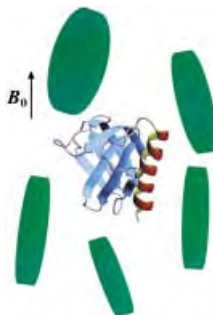
10 Years after Rio—Concepts on the  
Contribution of Chemistry to a  
Sustainable Development

**Keywords:** green chemistry •  
innovations • oxidations • renewable  
raw materials • sustainable development

## HIGHLIGHT

**The three-dimensional structures of biomacromolecules** in solution can be determined with NMR spectroscopy. The use of residual dipolar couplings (RDCs) that can be measured in dilute liquid crystalline solution is currently revolutionizing the way structures are determined by NMR spectroscopy. This is highlighted by the recent de novo structure determination of the protein ubiquitin (see picture; liquid crystals are shown in green) using only RDC data.

*Angew. Chem.* **2002**, *114*, 453–456



B. Simon, M. Sattler\* ..... 437–440

De Novo Structure Determination from  
Residual Dipolar Couplings by NMR  
Spectroscopy

**Keywords:** liquid crystals • NMR  
spectroscopy • protein structures •  
residual dipolar couplings • structure  
elucidation

## VIPs

The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.com>

Nonrelaxable Anisotropic Organization of Organic–Inorganic Hybrid Materials Induced by an Electric Field

G. Cerveau, R. J. P. Corriu,\*  
E. Framery, S. Ghosh, M. Nobili ◆

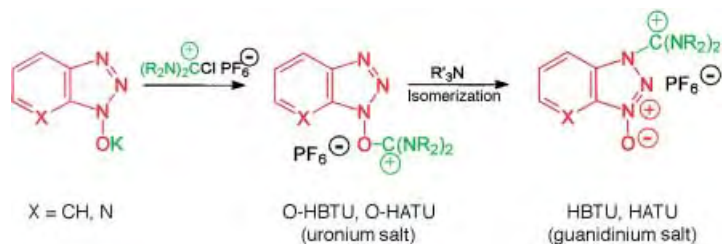
A Nanoporous Metal–Organic Framework Based on Bulky Phosphane Ligands

X. Xu, M. Nieuwenhuyzen,  
S. L. James\*

Surface Structure and Crystal Growth in Zeolite Beta C

B. Slater,\* R. A. Catlow, Z. Liu,  
T. Ohsuna, O. Terasaki,  
M. A. Camblor

**The strict exclusion of tertiary amines** during the otherwise standard synthetic approach to the synthesis of the guanidinium-type peptide coupling reagents HBTU ( $X = \text{CH}$ , see scheme) and HATU ( $X = \text{N}$ ) allows the synthesis of the uronium-type isomers of these guanidinium compounds, whose existence was until now pure speculation. These O isomers (O-HBTU and O-HATU) are more efficient coupling reagents than the N isomers.



*Angew. Chem.* **2002**, *114*, 457–461

L. A. Carpino,\* H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mügge, H. Wenschuh, J. Klose, M. Beyermann, M. Bienert ..... 441–445

The Uronium/Guanidinium Peptide Coupling Reagents: Finally the True Uronium Salts

**Keywords:** acylation • amides • amino acids • peptides • structure elucidation

**Covalent modifications of DNA** (DNA adducts, see schematic representation) play a key role in chemical carcinogenesis and are regarded as individual, internal dosimeters for exposure to genotoxic compounds. The analysis of DNA adducts has the potential to become an integral component of risk assessment.



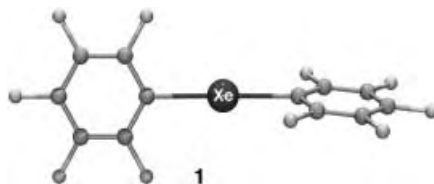
*Angew. Chem.* **2002**, *114*, 461–464

O. J. Schmitz,\* C. C. T. Wörth, D. Stach, M. Wiessler ..... 445–448

Capillary Electrophoresis Analysis of DNA Adducts as Biomarkers for Carcinogenesis

**Keywords:** DNA adduct • DNA damage • DNA methylation • electrophoresis • laser-induced fluorescence detection

**Despite the extreme instability** the organoxenon(II) compound  $\text{Xe}(\text{C}_6\text{F}_5)_2$  (**1**; see structure) was determined from X-ray powder diffraction data. Compound **1** crystallizes in the monoclinic space group  $P2_1/n$ , the C–Xe–C unit is linear, and the torsion angle of the  $\text{C}_6\text{F}_5$  rings is  $72.5^\circ$ . Experimental molecular parameters match well with calculated ones based on ab initio and density functional theory calculations.



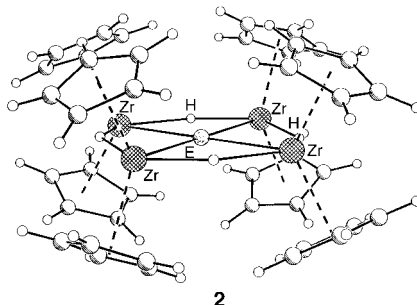
*Angew. Chem.* **2002**, *114*, 465–467

H. Bock, D. Hinz-Hübner, U. Ruschewitz,\* D. Naumann \* 448–450

Structure of Bis(pentafluorophenyl)-xenon,  $\text{Xe}(\text{C}_6\text{F}_5)_2$

**Keywords:** ab initio calculations • density functional calculations • noble gases • powder diffraction • structure elucidation • xenon

**Role change:** The arsenium salt  $\text{As}[\text{P}(\text{NMe}_2)_3]_2^+\text{BPh}_4^-$  (**1**), prepared for the first time, proved to be both an arsenic(III) and a phosphorus(III) source. Thus the reaction of **1** with  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  ( $\text{Cp} = \eta^5\text{-C}_5\text{H}_5$ ) leads not only to the first arsonium ion with anti-van't Hoff–Le Bel configuration **2a** ( $\text{E} = \text{As}$ ; see structure), but at the same time to the homologous phosphonium ion **2b** ( $\text{E} = \text{P}$ ).



*Angew. Chem.* **2002**, *114*, 467–470

M. Driess,\* H. Ackermann, J. Aust, K. Merz, C. von Wüllen ..... 450–453

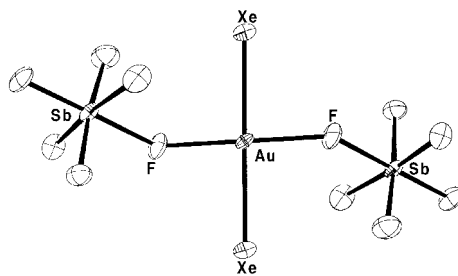
$\text{As}[\text{P}(\text{NMe}_2)_3]_2^+$  as Simultaneous  $\text{As}^{\text{I}}$  and  $\text{P}^{\text{I}}$  Source: Synthesis and Density Function Calculations of Planar Tetracoordinate Arsonium and Phosphonium Ions

**Keywords:** arsenic • density functional calculations • phosphorus • zirconium



**Complexes between precious metals and noble gases** are more abundant than was initially considered likely. For example, in addition to the already known  $[\text{AuXe}_4]^{2+}$  species, the cations *cis*- and *trans*- $[\text{AuXe}_2]^{2+}$  (whose structure is depicted),  $[\text{XeAuFAuXe}]^{3+}$ , and  $[\text{AuXe}_2\text{F}]^{2+}$  have been prepared and structurally characterized by X-ray crystallography in the form of their  $[\text{SbF}_6]^-$  or  $[\text{Sb}_2\text{F}_{11}]^-$  salts.

*Angew. Chem.* **2002**, *114*, 470–473



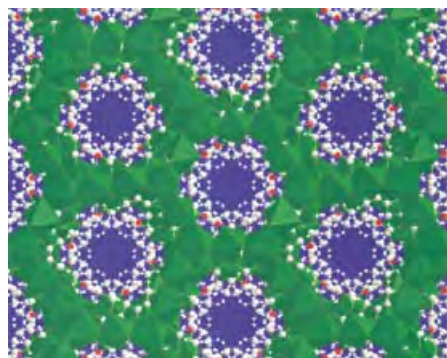
T. Drews, S. Seidel, K. Seppelt\* 454–456

Gold–Xenon Complexes

**Keywords:** coordination chemistry • gold • noble gases • xenon

**Hydrophobic, one-dimensional channels** with voids supported by a three-dimensional Ni–O–Ni framework occur in an open-framework modification of nickel succinate that was prepared by biphasic solvothermal synthesis and characterized by single-crystal X-ray diffraction (see picture; green:  $\text{NiO}_6$  octahedra, red: oxygen). The unbound and coordinated water molecules are shown to leave the structure above 200°C, and the structure persists to 425°C.

*Angew. Chem.* **2002**, *114*, 475–477



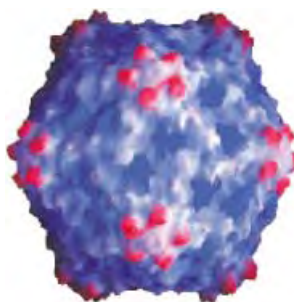
P. M. Forster,  
A. K. Cheetham\* ..... 457–459

Open-Framework Nickel Succinate,  
 $[\text{Ni}_7(\text{C}_4\text{H}_4\text{O}_4)_6(\text{OH})_2(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$ :  
A New Hybrid Material with Three-  
Dimensional Ni–O–Ni Connectivity

**Keywords:** carboxylate ligands • magnetic properties • microporous materials • nickel • zeolites

**Grow your nanochemical dendrimers!** Cowpea mosaic virus (see relief image derived from the X-ray structure) can be isolated from its host plant in gram quantities and participates in selective chemical reactions at specific sites of the icosahedrally-arrayed coat protein. Mutant structures can be easily engineered, propagated, and isolated to provide particles with tailored reactivities. Applications for these particles in areas from catalysis to materials science can be conceived.

*Angew. Chem.* **2002**, *114*, 477–480



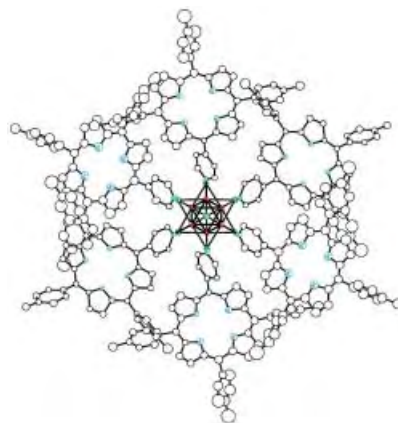
Q. Wang, T. Lin, L. Tang, J. E. Johnson,\*  
M. G. Finn\* ..... 459–462

Icosahedral Virus Particles as  
Addressable Nanoscale Building Blocks

**Keywords:** electron microscopy • polyvalency • viruses

**A porphyrin ball:** An octahedral arrangement of six porphyrins is achieved by the coordination of 5-(4-pyridyl)-10,15,20-tritolylporphyrins ( $\text{H}_2\text{PyT}_3\text{P}$ ) to the octa- $(\mu_3\text{-S}/\mu_3\text{-Se})$ hexarhenium(III) core. Six porphyrin ligands are arranged virtually in an  $S_6$  manner as the X-ray structural analysis of  $[\text{Re}_6(\mu_3\text{-S})_8(\text{H}_2\text{PyT}_3\text{P})_6](\text{SbF}_6)_2$  shows (see picture).

*Angew. Chem.* **2002**, *114*, 481–484

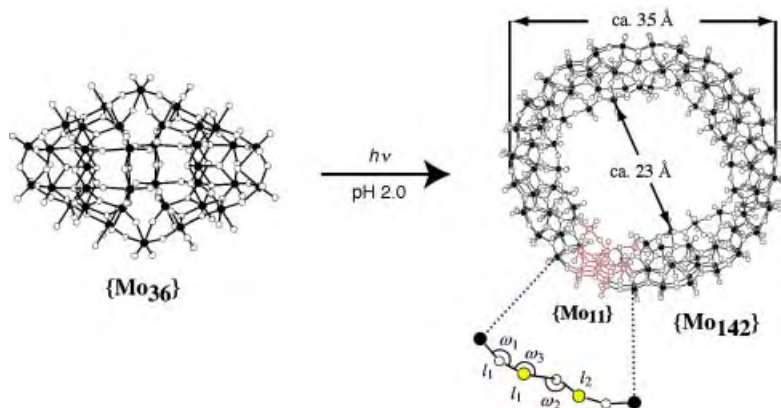


A. Itasaka, M. Abe, T. Yoshimura,  
K. Tsuge, M. Suzuki, T. Imamura,\*  
Y. Sasaki\* ..... 463–466

Octahedral Arrangement of Porphyrin  
Moieties around Hexarhenium(III) Cluster  
Cores: Structure of  $(\mu_3\text{-Selenido})\text{hexa-}$   
 $(5\text{-(4-pyridyl)-10,15,20-tritolylporphyrin})\text{-}$   
 $\text{hexarhenium(III)} (2+)$

**Keywords:** cluster compounds • porphyrinoids • rhenium • supramolecular chemistry

**Big blue-walled tires:** A diamagnetic blue 28-electron reduced species  $[\text{Mo}_{28}^{\text{V}}\text{Mo}_{114}^{\text{VI}}\text{O}_{432}\text{H}_{28}(\text{H}_2\text{O})_{58}]^{12-}$  ( $\{\text{Mo}_{142}\}$ ) was produced photochemically by the degradative self-assembly of  $[\text{Mo}_{36}\text{O}_{112}(\text{H}_2\text{O})_{16}]^{8-}$  ( $\{\text{Mo}_{36}\}$ ). The molybdenum blue photochemistry is not only suitable for the investigation of the mechanism of degradation self-assembly processes but also provides a basis for the molecular design of nanosized ring clusters.



*Angew. Chem.* **2002**, *114*, 484–487

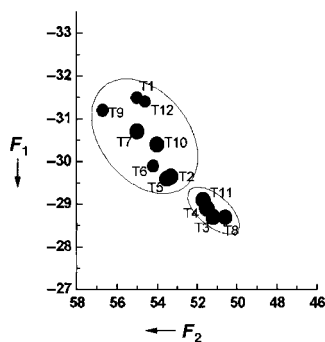
T. Yamase,\* P. V. Prokop ..... 466–469

Photochemical Formation of Tire-Shaped Molybdenum Blues: Topology of a Defect Anion,  $[\text{Mo}_{142}\text{O}_{432}\text{H}_{28}(\text{H}_2\text{O})_{58}]^{12-}$

**Keywords:** molybdenum • nanostructures • photochemistry • polyoxometalates • self-assembly



**Incorporation of Al atoms in particular sites** in the ZSM-5 structure is governed by the Si/Al ratio during synthesis, and their distribution over the twelve types of tetrahedral sites (T1–T12) during crystallization occurs in a nonrandom manner according to the results of  $^{27}\text{Al}$  MAS NMR measurements on a series of as-made ZSM-5 zeolites with Si/Al = 14–250. Further support for this conclusion was provided by  $^{27}\text{Al}$  MQMAS spectra (see picture) simulated with X-ray diffraction data.



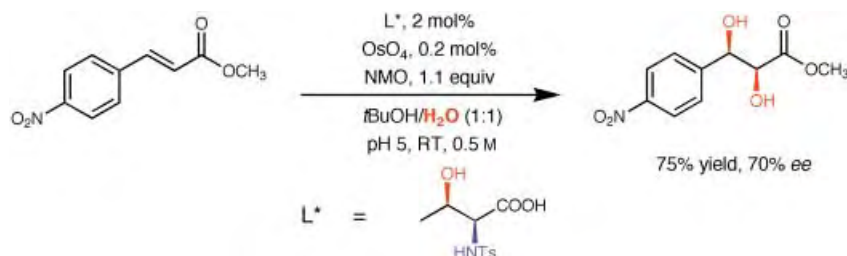
*Angew. Chem.* **2002**, *114*, 487–490

O. H. Han,\* C.-S. Kim, S. B. Hong\* ..... 469–472

Direct Evidence for the Nonrandom Nature of Al Substitution in Zeolite ZSM-5: An Investigation by  $^{27}\text{Al}$  MAS and MQ MAS NMR

**Keywords:** aluminosilicates • NMR spectroscopy • structure elucidation • zeolites

**Simple hydroxyamino acid derivatives act as chiral ligands** in osmium-catalyzed dihydroxylation and aminohydroxylation of olefins (see scheme). These are the first examples of asymmetric osmium-catalyzed processes proceeding in the second catalytic cycle with resident ligands on the metal center.



*Angew. Chem.* **2002**, *114*, 490–493

M. A. Andersson, R. Epple, V. V. Fokin,\* K. B. Sharpless\* ..... 472–475

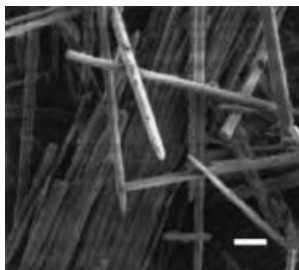
A New Approach to Osmium-Catalyzed Asymmetric Dihydroxylation and Aminohydroxylation of Olefins

**Keywords:** alkenes • aminohydroxylation • dihydroxylation • homogeneous catalysis • osmium



**The aluminophosphate molecular sieve  $\text{AlPO}_4\cdot 5$**  was prepared within a reverse microemulsion under hydrothermal conditions. The resulting crystals (see picture; scale 1  $\mu\text{m}$ ) display a novel fiberlike morphology with aspect ratios up to 100. The 100–200 nm thick fibers are aligned with the one-dimensional pores in the direction of the long axis of the fiber.

*Angew. Chem.* **2002**, *114*, 494–496

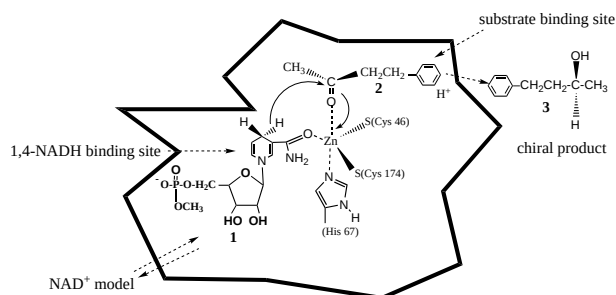


M. Z. Yates, K. C. Ott, E. R. Birnbaum, T. M. McCleskey \* ..... 476–478

Hydrothermal Synthesis of Molecular Sieve Fibers: Using Microemulsions To Control Crystal Morphology

**Keywords:** crystal growth • micelles • molecular sieves • surfactants • zeolite analogues

**Two tandem catalysis approaches:** first, a cofactor regeneration procedure with an  $\text{NAD}^+$  model and  $[\text{Cp}^*\text{Rh}(\text{bpy})\text{H}]^+$ , which was formed in situ, provided the 1,4-NADH analogue **1**. Cofactor **1** was then used with horse liver alcohol dehydrogenase (HLADH) for the conversion of prochiral ketones into chiral alcohols (e.g. **2**  $\rightarrow$  **3**).



*Angew. Chem.* **2002**, *114*, 496–499

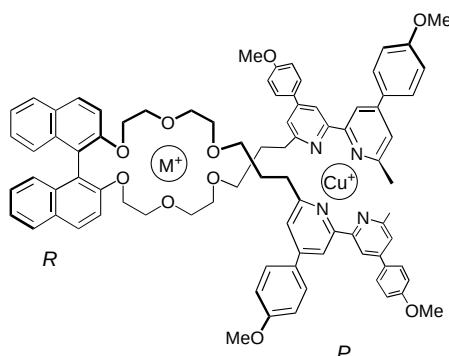
H. C. Lo, R. H. Fish \* ..... 478–481

Biomimetic  $\text{NAD}^+$  Models for Tandem Cofactor Regeneration, Horse Liver Alcohol Dehydrogenase Recognition of 1,4-NADH Derivatives, and Chiral Synthesis

**Keywords:** asymmetric synthesis • biomimetic synthesis • cofactors • enzyme catalysis • redox chemistry



**A significant enhancement** in the proportion of the (*P*)-helical enantiomer (see picture) of the tetrahedral copper(II)–bipyridine unit in a chiral pseudocrown ether occurs on complexation with an *achiral* alkali metal ion ( $\text{M}^+$ ). This dually responding system also works as an AND device for CD output by utilizing coordination and chiral information, with the  $\text{Cu}^+$  and  $\text{Na}^+$  ions acting as the input signals.



T. Nabeshima,\* A. Hashiguchi, T. Saiki, S. Akine ..... 481–484

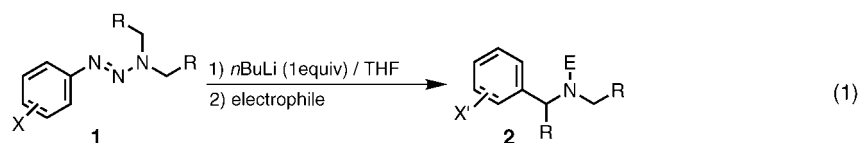
Transfer of Chiral Information through Achiral Ion Recognition by a Novel Pseudocrown Ether with a Binaphthyl Moiety

**Keywords:** host–guest systems • molecular devices • molecular recognition • receptors • supramolecular chemistry

*Angew. Chem.* **2002**, *114*, 499–502



**An alternative route to benzylamine derivatives** is provided by the lithiation of aryltriazenes followed by treatment with an electrophile [Eq. (1)]. The regioselectivity of the reaction can be controlled by means of the substituents X. When the 2- and 6-positions are substituted, tetrahydrobenzotriazines are obtained.



*Angew. Chem.* **2002**, *114*, 502–504

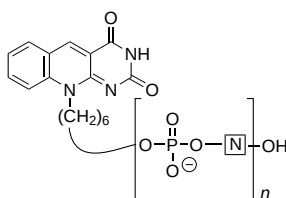
K. Nishiwaki,\* T. Ogawa, K. Matsuo \* ..... 484–486

$\alpha$ -Lithiation of 1-Aryl-3,3-dialkyltriazenes and Intramolecular Conversion to Benzylamine and Tetrahydrobenzotriazine Derivatives

**Keywords:** amines • C–C coupling • dearomatization • nitrogen heterocycles • nucleophilic addition



**Dramatic quenching of fluorescence** is observed both in solution and on a glass surface during hybridization of deazaflavin–oligonucleotide conjugates (see picture, [N] = nucleoside) to a complementary strand. This opens up the possibility of a new type of DNA microarray, in which the fluorophore is on the probe and not on the target, with the advantage of possible control over the quality of the array.



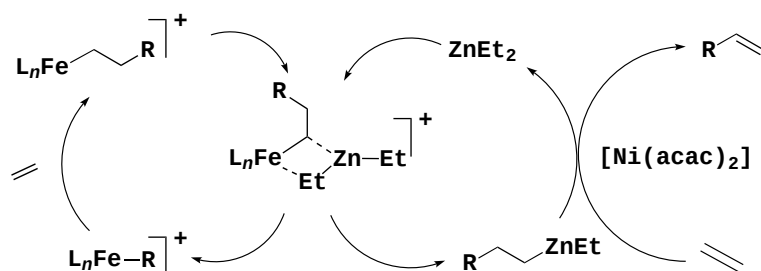
C. Dueymes, J. L. Décout,\* P. Peltié,  
M. Fontecave\* ..... 486–489

Fluorescent Deazaflavin–  
Oligonucleotide Probes for Selective  
Detection of DNA

**Keywords:** DNA recognition • flavins •  
fluorescence • hybridization •  
oligonucleotides

Angew. Chem. 2002, 114, 504–507

**Bis(imino)pyridineiron complexes** are not only highly active for ethylene polymerization, they are shown to catalyze efficient polyethylene chain growth at zinc centers—formally an iron-catalyzed *Aufbaureaktion* on zinc (see scheme). The grown alkyl chains can be displaced from the zinc centers by an olefin exchange reaction catalyzed by, for example, [Ni(acac)<sub>2</sub>] (acac = acetylacetonate) to give linear  $\alpha$ -olefins with a Poisson distribution.



G. J. P. Britovsek, S. A. Cohen,  
V. C. Gibson,\* P. J. Maddox,  
M. van Meurs ..... 489–491

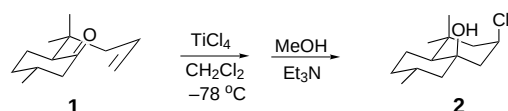
Iron-Catalyzed Polyethylene Chain  
Growth on Zinc: Linear  $\alpha$ -Olefins with a  
Poisson Distribution

**Keywords:** alkenes • iron •  
polymerization • zinc

Angew. Chem. 2002, 114, 507–509



**Monocyclic and acyclic ketones** bearing  $\delta,\epsilon$ - and  $\epsilon,\zeta$ -unsaturated side chains such as pulegone derivative **1** undergo *syn*-selective cyclizations with TiCl<sub>4</sub> to form *cis*-1,3-chlorohydrins **2**.



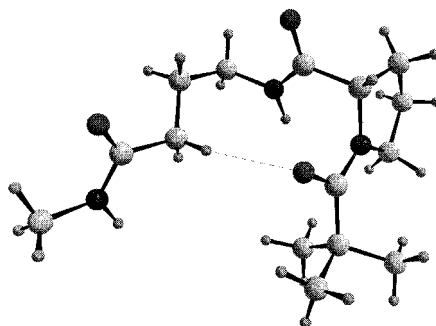
C. E. Davis, R. M. Coates\* .... 491–493

Stereoselective Prins Cyclizations of  $\delta,\epsilon$ -  
Unsaturated Ketones to *cis*-3-  
Chlorocyclohexanols with TiCl<sub>4</sub>

**Keywords:** chlorohydrins • cyclization •  
diastereoselectivity • electrophilic  
additions • terpenoids

Angew. Chem. 2002, 114, 509–511

**Similar to the classical  $\beta$  turn:** An intramolecular cyclic 10-atom motif is defined in the molecular conformation of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe (see powder X-ray diffraction structure; Piv: pivaloyl, <sup>1</sup>pro: L-proline,  $\gamma$ -Abu:  $\gamma$ -aminobutyric acid) by a C–H $\cdots$ O interaction. This study emphasizes the considerable potential of powder X-ray diffraction as an alternative to single-crystal X-ray diffraction.



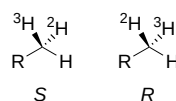
E. Y. Cheung, E. E. McCabe,  
K. D. M. Harris,\* R. L. Johnston,  
E. Tedesco, K. M. P. Raja,  
P. Balaram\* ..... 494–496

C–H $\cdots$ O Hydrogen Bond Mediated  
Chain Reversal in a Peptide Containing a  
 $\gamma$ -Amino Acid Residue, Determined  
Directly from Powder X-ray Diffraction  
Data

**Keywords:** hydrogen bonds • peptides •  
powder diffraction • structure  
elucidation • X-ray diffraction

Angew. Chem. 2002, 114, 512–514

**Only non-enzymatic transformations** were used to synthesize chiral *N,N*-ditosylmethylamine (see picture). This facile and convenient synthesis allows access to both enantiomers of the methyl group in an enantiomeric ratio of 83:17.



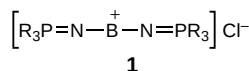
N. Faucher, J.-C. Cintrat,\* P. Berthault,  
B. Rousseau\* ..... 497–498

The Shortest Route to Chiral  
Ditosylmethylamine

**Keywords:** deuterium •  
enantioselectivity • hydrides • isotopic  
labeling • tritium

*Angew. Chem.* **2002**, *114*, 515–516

**A linear arrangement of the P-N-B-N-P linkage** occurs in the unique extended structure of the cation of the borinium salt **1**, which was obtained from the reaction of  $[\text{tBu}_3\text{PN}]\text{Li}$  with  $\text{BCl}_3$ . The related species  $(\text{tBu}_3\text{PN})_2\text{BH}$  was also prepared and shown to react with  $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$  to afford the analogous salt  $[(\text{tBu}_3\text{PN})_2\text{B}][\text{B}(\text{C}_6\text{F}_5)_4]$ . NMR data and ab initio computations infer that tight ion pairing occurs for **1** in nonpolar solvents.



S. Courtenay, J. Y. Mutus, R. W. Schurko,  
D. W. Stephan\* ..... 498–501

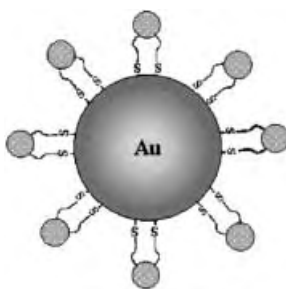
The Extended Borinium  
Cation:  $[(\text{tBu}_3\text{PN})_2\text{B}]^+$

**Keywords:** boranes • boron • cations •  
N ligands • phosphinimide ligands

*Angew. Chem.* **2002**, *114*, 516–519



**Functionalization of  $\gamma\text{-[SiW}_{10}\text{O}_{36}]^{8-}$**  with the sulfanylalkylsilane  $\text{HSC}_3\text{H}_6\text{Si}(\text{OMe})_3$  affords difunctionalized  $\gamma\text{-[SiW}_{10}\text{O}_{36}(\text{HSC}_3\text{H}_6\text{Si})_2\text{O}]^{4-}$ , which on addition to colloidal solutions of gold nanoparticles (4–12 nm) forms a novel hybrid nanosystem (see schematic diagram).



C. R. Mayer, S. Neveu,  
V. Cabuil\* ..... 501–503

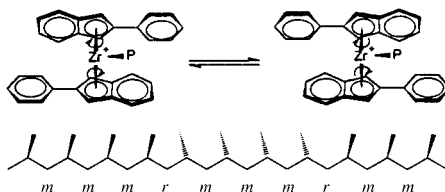
A Nanoscale Hybrid System Based on  
Gold Nanoparticles and  
Heteropolyanions

**Keywords:** colloids • gold •  
polyoxometalates

*Angew. Chem.* **2002**, *114*, 519–521



**Rather than involving the *rac*-like (chiral) and *meso*-like (achiral) conformations**, as commonly believed, the “oscillation” of  $[(2\text{-Ar-indenyl})_2\text{ZrCl}_2]$  propene polymerization catalysts takes place *within* the *rac*-like conformation, between its two enantiomorphous forms with opposite enantioselectivities. The result is the peculiar polypropylene microstructure shown, which degenerates into a (quasi)-atactic form when the “oscillation” is faster than monomer insertion.



V. Busico,\* R. Cipullo, W. P. Kretschmer,  
G. Talarico, M. Vacatello,  
V. Van Axel Castelli ..... 505–508

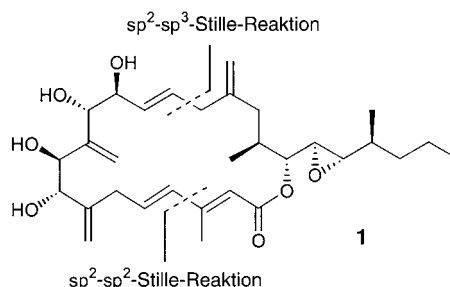
“Oscillating” Metallocene Catalysts: How  
Do They Oscillate?

**Keywords:** homogeneous catalysis •  
metallocenes • oscillating metallocenes •  
polymerization • polypropylene •  
reaction mechanisms

*Angew. Chem.* **2002**, *114*, 523–526



**Judicious use of both inter- and intramolecular Stille reactions** was required in the synthesis of **1**, the putative stereostructure of amphidinolide A. Compound **1** was shown to be a diastereomer of the natural product.



H. W. Lam, G. Pattenden\* .... 508–511

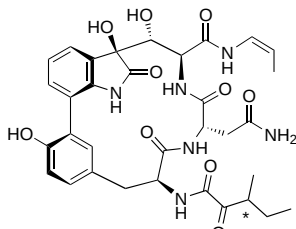
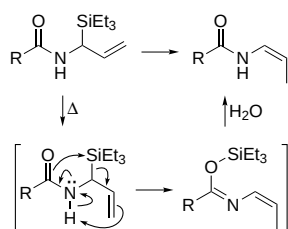
Total Synthesis of the Presumed  
Amphidinolide A

**Keywords:** cross-coupling • macrocycles •  
macrolides • Stille reaction •  
total synthesis

*Angew. Chem.* **2002**, *114*, 526–529



**Silatropic and ene-like bond reorganizations** (see scheme, left) were the key steps in the first total synthesis of the title compounds, which only differ in stereochemistry at the remote C36 stereocenter. Other key steps include a Suzuki biaryl construction, a diastereofacial dihydroxylation reaction, and a macrolactamization.



TMC-95A/TMC-95B

*Angew. Chem.* **2002**, *114*, 530–533

S. Lin, S. J. Danishefsky\* ..... 512–515

The Total Synthesis of Proteasome Inhibitors TMC-95A and TMC-95B: Discovery of a New Method To Generate *cis*-Propenyl Amides

**Keywords:** biaryls • inhibitors • macrolactamization • rearrangement • total synthesis



Supporting information on the WWW (see article for access details).

\* Author to whom correspondence should be addressed



Accelerated publications



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| <b>Capillary Electrochromatography</b>               | Keith D. Bartle, Peter Myers       | <i>F. Steiner</i> ..... 519  |
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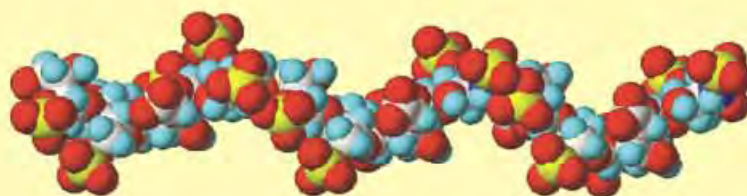
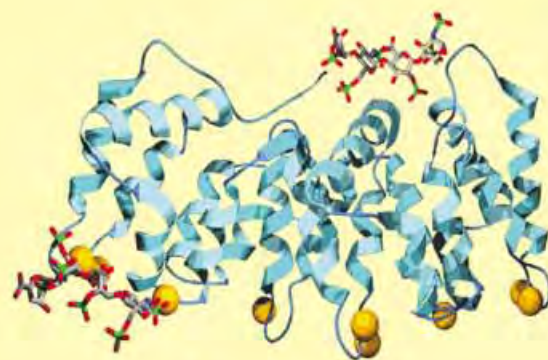
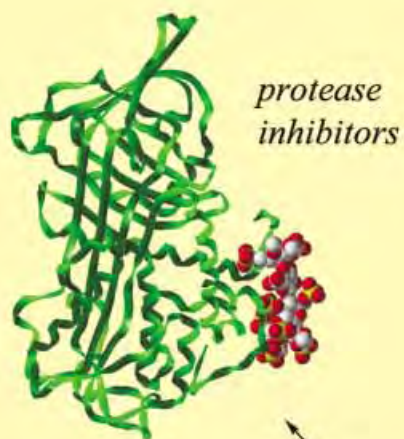
Issue 2, 2002 was published online on January 18.

## CORRIGENDA

The Communication by **G. M. Whitesides and co-workers** in Issue 12, 2001, pp. 2316–2320 should have referenced a paper that was published at approximately the same time and contained some of the same experimental data: R. E. Holmlin, R. Haag, M. L. Chabiny, R. F. Ismagilov, A. E. Cohen, A. Terfort, M. A. Rampi, G. M. Whitesides, *J. Am. Chem. Soc.* **2001**, *123*, 5075–5085 (“Electron Transport through Thin Organic Films in Metal-Insulator-Metal Junctions Based on Self-Assembled Monolayers”). This full paper gives the details of the largest part of the experimental work communicated in *Angewandte Chemie*. Omission of this reference gave the impression of “duplicate publication”, for which the authors apologize to both journals. The acknowledgement should also have listed the affiliation of Dr. Andreas Terfort as the Institute for Inorganic and Applied Chemistry, University of Hamburg, Germany.

In the Communication by **D. Xiao** and **X. Zhang** in Issue 18, 2001, pp. 3425–3428, one of the authors' names was misspelled and should be Dengming Xiao.

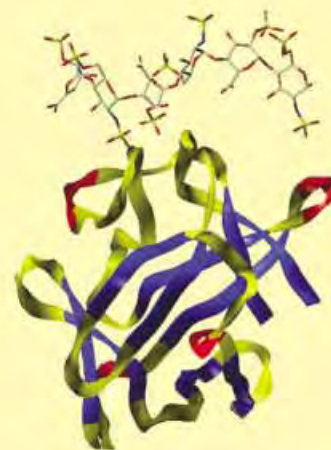
The hydantoinase enzyme referred to in Section 3.3 of the Review by **K. Powell et al.** in Issue 21, 2001, pp. 3949–3959 was evolved by using error-prone polymerase chain reaction (PCR). The enzyme, which is jointly patented by Caltech and Degussa, is used in the production of L-methionine by Degussa. The authors apologize for the error.



## *Heparin-Protein Interactions*



*viral envelope proteins*



*growth factors*

# Heparin – Protein Interactions

Ishan Capila and Robert J. Linhardt\*

Heparin, a sulfated polysaccharide belonging to the family of glycosaminoglycans, has numerous important biological activities, associated with its interaction with diverse proteins. Heparin is widely used as an anticoagulant drug based on its ability to accelerate the rate at which antithrombin inhibits serine proteases in the blood coagulation cascade. Heparin and the structurally related heparan sulfate are complex linear polymers comprised of a mixture of chains of different length, having variable sequences. Heparan sulfate is ubiquitously distributed on the surfaces of animal cells and in the extracellular matrix. It also mediates

various physiologic and pathophysiologic processes. Difficulties in evaluating the role of heparin and heparan sulfate in vivo may be partly ascribed to ignorance of the detailed structure and sequence of these polysaccharides. In addition, the understanding of carbohydrate–protein interactions has lagged behind that of the more thoroughly studied protein–protein and protein–nucleic acid interactions. The recent extensive studies on the structural, kinetic, and thermodynamic aspects of the protein binding of heparin and heparan sulfate have led to an improved understanding of heparin–protein interactions. A high degree of

specificity could be identified in many of these interactions. An understanding of these interactions at the molecular level is of fundamental importance in the design of new highly specific therapeutic agents. This review focuses on aspects of heparin structure and conformation, which are important for its interactions with proteins. It also describes the interaction of heparin and heparan sulfate with selected families of heparin-binding proteins.

**Keywords:** carbohydrates • coagulation • heparin • medicinal chemistry • molecular recognition

## 1. Introduction

### 1.1. Historical Perspective on Heparin

Heparin, an anticoagulant drug, is widely recognized to be a biologically important and chemically unique polysaccharide. Heparin was discovered in 1916 by Jay McLean, a second-year medical student, working under the direction of physiologist William Howell at Johns Hopkins University.<sup>[1]</sup> An understanding of heparin's structure developed gradually. In 1928 Howell correctly identified one of the sugars in heparin to be a uronic acid,<sup>[2]</sup> and in 1935–1936 Jorpes and Bergstrom found glucosamine to be the second sugar component in heparin.<sup>[3]</sup> Jorpes and later Charles established that heparin contained a high level of covalently linked sulfate making it one of the strongest acids in nature.<sup>[4]</sup> Subsequent studies also identified the 1→4-linkage between C-1 of glucosamine and C-4 of the uronic acid and the location of the *O*-sulfo groups.<sup>[1]</sup> The

uronic acid was confirmed to be L-iduronic acid by Perlin et al. in 1968 using NMR spectroscopy.<sup>[5]</sup> Thus, heparin finally emerged as a sulfated, linear polysaccharide with a repeating disaccharide unit containing iduronic acid and glucosamine.

By 1935, enough heparin of satisfactory purity had been prepared by Jorpes in Sweden, in collaboration with Charles and Scott in Canada, to allow clinical testing. The effectiveness of heparin treatment in the prevention of postoperative thrombosis was quickly established through the work of Crafoord and Best,<sup>[6]</sup> and this medical practice continues to this day. However, using heparin also leads to undesirable side effects, such as bleeding complications or heparin-induced thrombocytopenia (HIT). These complications, an improved understanding of the coagulation cascade, and the fractionation of heparin led to the development of low-molecular-weight (LMW) heparin fractions with better defined chemical and biological properties.<sup>[7]</sup> These agents have more predictable pharmacological actions, sustained activity, improved bioavailability and a better therapeutic index ( $ED_{50}/LD_{50}$ ). Thus, at the beginning of the new millennium, LMW heparins have displaced heparin as the major clinical anticoagulant.<sup>[8]</sup>

In 1973, Rosenberg and Damus suggested that heparin binds to antithrombin, causing a conformational change within antithrombin III (AT III) leading to a greatly accel-

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erated reaction with thrombin and the formation of an inactive complex of the two proteins.<sup>[9]</sup> Affinity fractionation helped in the identification of the minimal sequence in heparin required for binding AT III.<sup>[10]</sup> The interaction of heparin with antithrombin was the first reported case of a specific heparin–protein interaction of physiological significance. Over the past two decades a growing number of biological activities have been discovered to be regulated by the interaction of heparin and heparan sulfate with heparin-binding proteins.<sup>[11]</sup> These interactions play important roles in the normal physiological as well as pathological processes.

The connection of our laboratory to this field started with studies on the purification of the heparin lyases from a soil bacterium, *Flavobacterium heparinum*, and the characterization of their substrate specificity.<sup>[12, 13]</sup> To study the action of these enzymes we needed to develop new methods for the isolation, purification and structural characterization of heparin- and heparan-sulfate-derived oligosaccharides.<sup>[14]</sup> The preparation of these structurally defined pure oligosaccharides represented a breakthrough in understanding heparin's interaction with proteins and in determining the precise structural requirements within heparin essential for each interaction.

## 2. Heparin

### 2.1. Structure of Heparin and Heparan Sulfate

Heparin is a linear polymer consisting of repeating units of 1→4-linked pyranosyluronic acid and 2-amino-2-deoxyglucopyranose (glucosamine) residues.<sup>[15]</sup> The uronic acid resi-

dues typically consist of 90% L-idopyranosyluronic acid (L-iduronic acid) and 10% D-glucopyranosyluronic acid (D-glucuronic acid). Heparin has the highest negative charge density of any known biological macromolecule. This is the result of its high content of negatively charged sulfo and carboxyl groups.<sup>[6]</sup> Indeed, the average heparin disaccharide contains 2.7 sulfo groups. The most common structure occurring in heparin is the trisulfated disaccharide (Scheme 1). However, a number of structural variations of this disaccharide exist, leading to the microheterogeneity of heparin. The amino group of the glucosamine residue may be substituted with an acetyl or sulfo group or unsubstituted. The 3- and 6-positions of the glucosamine residues can either be substituted with an O-sulfo group or unsubstituted. The uronic acid, which can either be L-iduronic or D-glucuronic acid, may also contain a 2-O-sulfo group. Glycosaminoglycan heparin has a molecular weight range of 5–40 kDa, with an average molecular weight of about 15 kDa and an average negative charge of approximately –75. The molecular weight distribution ( $M_w/M_n$ ) of heparin corresponds to its polydispersity. This structural variability makes heparin an extremely challenging molecule to characterize.

The structural complexity of heparin can be considered at several levels. At the proteoglycan (PG) level, different numbers of polysaccharide (or glycosaminoglycan) chains (possibly having different saccharide sequences) can be attached to the various serine residues present in heparin's core protein. During their biosynthesis, heparin chains are

[\*] In this review, the common prefixes sulfo and carboxyl are used instead of sulfonato and carboxylato as recommended by the IUPAC publication *Nomenclature of Carbohydrates*.

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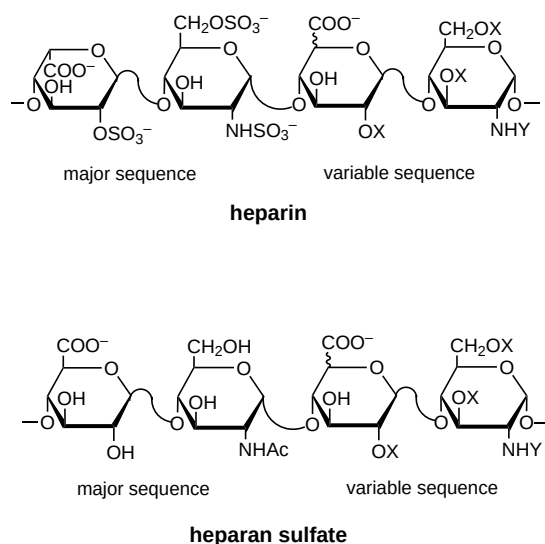


I. Capila



R. J. Linhardt

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Scheme 1. Major and minor disaccharide repeating units in heparin and heparan sulfate (X = H or SO<sub>3</sub><sup>-</sup>, Y = Ac, SO<sub>3</sub><sup>-</sup>, or H).

attached to a unique core protein, serglycin, found only in mast cells and some hematopoietic cells. Tissue proteases act on this core protein to release peptidoglycan heparin, a small peptide to which a single long polysaccharide chain (100 kDa) is attached. This peptidoglycan is short-lived as it is immediately processed by a  $\beta$ -endoglucuronidase to a number of smaller (ca. 15 kDa) polysaccharide chains called glycosaminoglycan (GAG) heparin.<sup>[11]</sup> Most of the chemical and physical properties of heparin are related to GAG structure or sequence, conformation, chain flexibility, molecular weight, and charge density.

Heparan sulfate is structurally related to heparin but is much less substituted with sulfo groups than heparin and has a more varied structure (or sequence). Like heparin, heparan sulfate is a repeating linear copolymer of a uronic acid 1→4-linked to glucosamine (Scheme 1).<sup>[16]</sup> While D-glucuronic acid predominates in heparan sulfate, it can contain substantial amounts of L-iduronic acid. Heparan sulfates generally contain only about one sulfo group per disaccharide, but individual heparan sulfates may have higher contents of this group. Heparan sulfate chains also often contain domains of extended sequences having low or high sulfation.<sup>[17]</sup> While heparan sulfate contains all of the structural variations found in heparin (and vice versa), the frequency of occurrence of the minor sequence variants is greater than in hep-

arin, making heparan sulfate's structure and sequence much more complex. Heparan sulfate chains are also polydisperse, but are generally longer than heparin chains, having average molecular weight of about 30 kDa ranging from 5 to 50 kDa.<sup>[18]</sup>

Heparan sulfate is biosynthesized, as a proteoglycan, through the same pathway as heparin, however, unlike heparin, the heparan sulfate GAG chain remains connected to its core protein. Heparan sulfate is ubiquitously distributed on cell surfaces and is also a common component of the extracellular matrix.<sup>[17, 19]</sup> Two types of core proteins, the syndecans (an integral membrane protein) and the glypicans (a GPI-anchored protein), commonly carry heparan sulfate GAG chains and correspond to the two major families of heparan sulfate proteoglycans (heparan sulfate PGs).<sup>[19, 20]</sup> The heparan sulfate chains on these heparan sulfate PGs bind a variety of proteins and mediate various physiologically important processes including, blood coagulation, cell adhesion, lipid metabolism, and growth factor regulation.<sup>[21]</sup> Although structurally similar, heparin and heparan sulfate GAGs can often be structurally distinguished through their different sensitivity towards a family of GAG-degrading, microbial enzymes, the heparin lyases.<sup>[22]</sup> In the following sections, most of the properties that we discuss with respect to heparin are also applicable, except where specified, to heparan sulfate.

## 2.2. Conformation of Heparin

Heparin is a linear, unbranched, highly sulfated polysaccharide that exists primarily as a helical structure (Figure 1).<sup>[23]</sup> Unlike proteins, heparin is not known to display or fold into any particular tertiary structure. The specificity of its interactions with a diverse range of biologically important

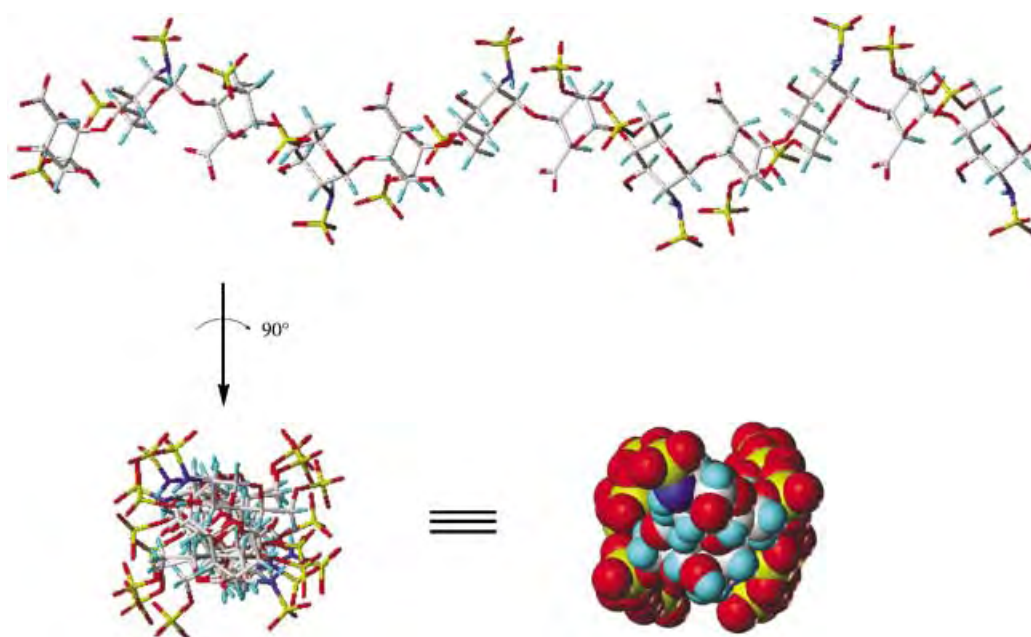


Figure 1. Helical conformation of a heparin dodecasaccharide sequence having the major disaccharide repeating structure shown in Scheme 1 with sulfur atoms (yellow), oxygen atoms (red), nitrogen atoms (blue) and hydrogen atoms (cyan).

proteins suggests that it displays its sulfo and carboxyl groups in defined patterns and orientations to promote specific protein interactions.<sup>[24]</sup> The conformational flexibility of the L-iduronic acid residue within heparin is believed to be responsible for the wide range of specific protein interactions exhibited by this family of GAGs.<sup>[25]</sup>

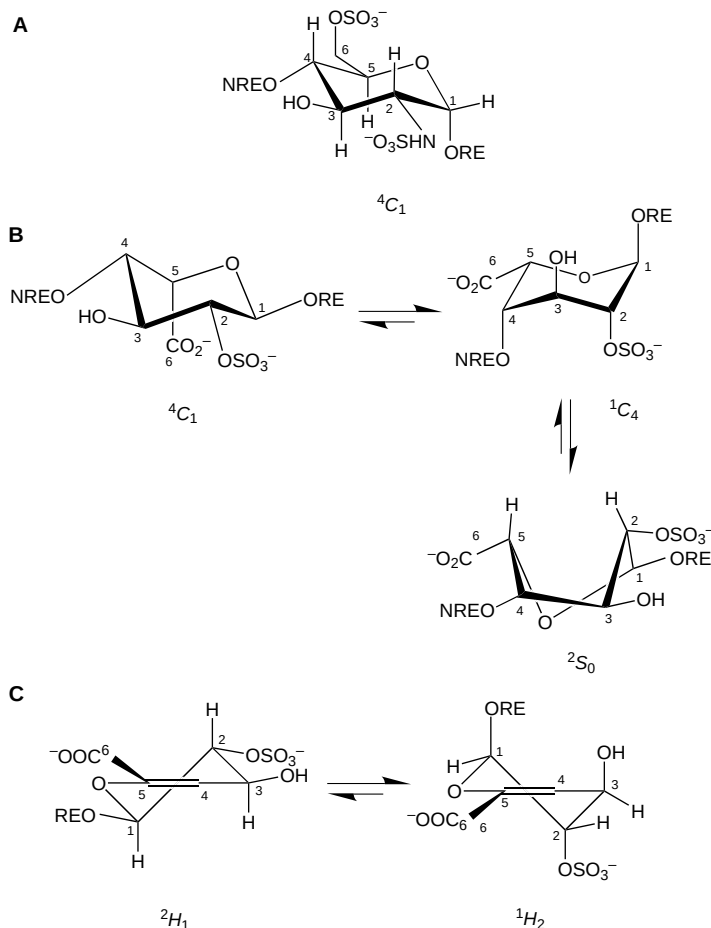
Analysis of the conformation of individual sugars within heparin indicates that the D-glucosamine and D-glucuronic acid residues assume the preferred  ${}^4C_1$  conformation (Scheme 2A).<sup>[26]</sup> The conformation of the flexible L-iduronic acid (IdoA) residue varies, depending on the substitution pattern

and skew boat forms.<sup>[29]</sup> The  ${}^2S_0$  form appears to be slightly favored in terms of conformational stability, as it tends to minimize the unfavorable 1,3 diaxial nonbonded interactions that are expected in the  ${}^1C_4$  form, where four of the substituents are axially oriented and only the carboxyl group is equatorial.<sup>[30]</sup> However, the energy barrier to the  ${}^1C_4$  form is not high, and so it is possible for the iduronate ring to change between the  ${}^2S_0$  and  ${}^1C_4$  forms so that in the protein-bound state it can make favorable electrostatic interactions with basic amino acids on the protein.

Indeed, while the spatial orientation of the 2-O-sulfo group in the IdoAp2S residues is altered during  ${}^1C_4$ – ${}^2S_0$  interconversion, no significant conformational change in the backbone of the polysaccharide chain takes place.<sup>[23]</sup> The crystal structure analysis of FGF-2 bound to a heparin hexasaccharide revealed that one internal IdoAp2S residue makes contact with the protein and resides in a  ${}^1C_4$  conformation while the other makes contact in the  ${}^2S_0$  conformation.<sup>[31]</sup> Thus, while the iduronate rings are flexible and in equilibrium between the  ${}^2S_0$  and  ${}^1C_4$  conformation in the unbound state, they can be locked into either conformation when bound to a protein. The prevalence for one iduronate conformer is influenced by the substitution pattern of the D-glucosamine residue bound to its non-reducing end. For example, when the IdoAp2S residue has a N-acetylglucosamine (D-GlcNpAc) substituted at its 4-position, it resides almost exclusively in the  ${}^1C_4$  chair conformer.<sup>[32]</sup>

Despite the conformational flexibility of the L-iduronate residues, heparin saccharides show relatively conserved angles  $\phi$  and  $\psi$  in glycosidic linkages. NMR studies on a series of modified heparins with systematically altered substitution patterns indicate that all derivatives, regardless of sulfation pattern, exhibit similar glycosidic bond conformations.<sup>[33]</sup> The helical parameters for heparin oligosaccharides bound to fibroblast growth factors have been determined by X-ray crystallography, and these values are comparable.<sup>[31, 34]</sup>

Homogenous, structurally defined heparin and heparan sulfate oligosaccharides are commonly enzymatically prepared from these GAGs using heparin lyases.<sup>[14]</sup> These enzymes break down heparin into oligosaccharides that contain a nonreducing terminal 4-deoxy- $\alpha$ -L-threo-2-sulfohex-4-enopyranosyluronic acid ( $\Delta^4$ -uronic acid,  $\Delta$ UAp2S) residue.<sup>[35]</sup> Understanding the conformation of these residues is important when using these oligosaccharides to study heparin–protein interactions and also to understand the unusual reactivity of these  $\Delta^4$ -uronates.<sup>[36, 37]</sup> Based on the conformation about the 4,5-double bond, the  $\Delta$ UAp2S residue can exist in either the  ${}^2H_1$  or  ${}^1H_2$  forms (Scheme 2C), and the equilibrium between these two conformers is controlled by their substitution pattern.<sup>[37, 38]</sup> Crystallographic data also show that these two forms coexist within the same unit cell, suggesting that they are nearly equal in energy.<sup>[39]</sup> However, the solution structures of heparin-derived oligosaccharides determined by NMR spectroscopy suggest that the terminal  $\Delta$ UAp2S residue is predominantly represented by the  ${}^1H_2$  form with minor contribution from the  ${}^2H_1$  form.<sup>[29, 30]</sup>



Scheme 2. Conformational flexibility of residues in heparin and heparan sulfate. A) The predominant  ${}^4C_1$  form of glucosamine. B)  ${}^4C_1$ ,  ${}^1C_4$ , and  ${}^2S_0$  conformers of IdoA. C)  ${}^2H_1$  and  ${}^1H_2$  forms of the  $\Delta^4$ -uronic acid at the nonreducing end. RE and NRE correspond to the reducing and the nonreducing end of a saccharide sequence, respectively.

of this residue and on its relative position in the chain. When the IdoA residue is at the reducing end of an oligosaccharide, NMR data suggest three possible conformers, the  ${}^4C_1$  and  ${}^1C_4$  chair and the  ${}^2S_0$  skew boat (Scheme 2B).<sup>[27]</sup> When the IdoA residue is internal, only two conformations, the  ${}^1C_4$  chair and the  ${}^2S_0$  skew boat are accessible.<sup>[28]</sup> For the 2-O-sulfo- $\alpha$ -L-idopyranosylurionate (IdoAp2S) residue also these same two conformations are accessible, and solution NMR studies on a heparin-derived hexasaccharide show that the internal IdoAp2S residues exist in equilibrium between the chair

### 2.3. Biosynthesis of Heparin

The biosynthesis of heparin and heparan sulfate and the regulatory mechanisms resulting in the placement of different saccharide sequences in their structures are only partly understood (Scheme 3). Studies on heparin biosynthesis were carried out in a mastocytoma cell culture system with radiolabeled metabolic precursors of heparin.<sup>[40, 41]</sup> The core protein, serglycin, contains a high number of serine and glycine repeats and is primarily synthesized in the rough endoplasmic reticulum.

The biosynthesis of the GAG chain predominantly takes place in the Golgi apparatus. The first step in the pathway involves the attachment of a tetrasaccharide fragment to a serine residue in the core protein.<sup>[42]</sup> The sequence of this linkage-region tetrasaccharide is  $\beta$ -GlcAp(1 $\rightarrow$ 3)- $\beta$ -Galp(1 $\rightarrow$ 3)- $\beta$ -Galp(1 $\rightarrow$ 4)- $\beta$ -Xylp-1 $\rightarrow$ Ser. There are four glycosyltransferases responsible for the synthesis of the linkage region.<sup>[43]</sup> The glucuronyltransferase that attaches the terminal glucuronic acid (GlcAp)<sup>[44]</sup> and the galactosyltransferase that attaches the second galactose (Galp) residue<sup>[45]</sup> have been cloned and characterized. Onto this neutral sugar linkage region the first GlcNpAc residue or *N*-acetylgalactosamine (GalNpAc, in the biosynthesis of chondroitin sulfates) is added. This addition decides whether the chain will either be a glucosaminoglycan (heparin and heparan sulfate) or a galactosaminoglycan (chondroitin sulfate/dermatan sulfate). It has been suggested that peptide sequence motifs close to the linkage-region substituted serine residues act as a signal for the addition of a GlcNpAc residue, thus initiating heparin/heparan sulfate formation; and an  $\alpha$ -GlcNpAc transferase believed to catalyze this reaction has been identified.<sup>[46]</sup>

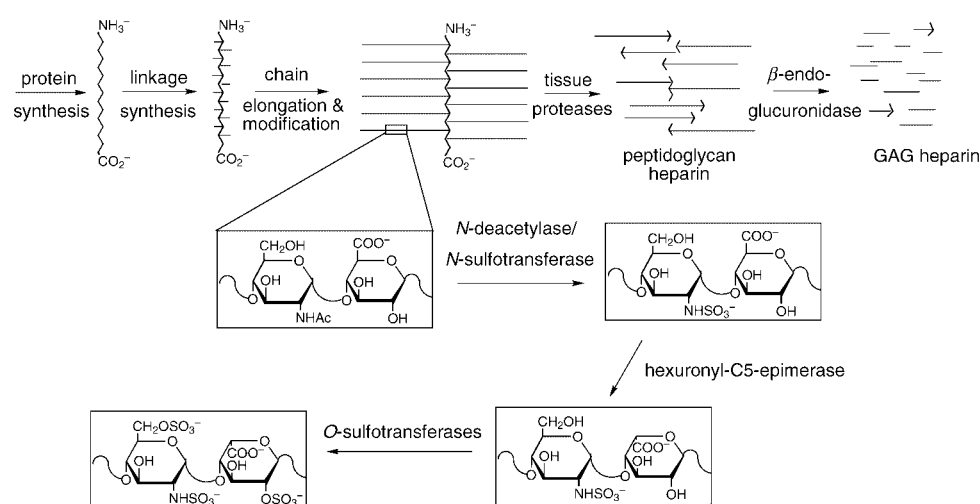
After the first residue has been added, alternating transfer of GlcAp and GlcNpAc residues from their corresponding UDP-sugar nucleotides to the nonreducing termini of growing chains forms the rest of the GAG chain. It is believed that one enzyme, formed by a hetero-oligomeric complex of two

proteins (EXT1 and EXT2), has both GlcAp transferase and GlcNpAc transferase activity.<sup>[47]</sup> Approximately 300 sugar residues are added to the linear polysaccharide chain before its synthesis terminates.<sup>[40]</sup> As the chain elongates it also undergoes other modification reactions.<sup>[48]</sup> Modification of the polymer is initiated by *N*-deacetylation and *N*-sulfation of the GlcNpAc residues by an *N*-deacetylase/*N*-sulfotransferase enzyme. Subsequent steps occur sequentially and either on or adjacent to the *N*-sulfoglucosamine (GlcNpS)-containing residue. A C-5 epimerase then catalyzes transformation of some of the D-glucuronic acid residues to L-iduronic acid residues.<sup>[49]</sup> This is followed by O-sulfation of the iduronic acid residues at the C-2 position by an iduronosyl 2-*O*-sulfotransferase. It has been shown that the IdoAp in an IdoAp  $\rightarrow$  GlcNpS disaccharide can be sulfated by this enzyme provided the GlcNpS residue does not contain an *O*-sulfo group at the C-6 position.<sup>[50]</sup> Studies have also shown that a very active glucuronosyl 2-*O*-sulfotransferase, in mouse mastocytoma microsomal fractions, is responsible for the O-sulfation of GlcAp residues at the C-2 position.<sup>[51]</sup> There is also evidence suggesting that the glucuronosyl 2-*O*-sulfotransferase is the same enzyme as the iduronosyl 2-*O*-sulfotransferase.<sup>[52]</sup> The 2-*O*-sulfation of the uronic acid is followed by the action of glucosamine 6-*O*-sulfotransferase, which transfers an *O*-sulfo group to the C-6 position of GlcNpAc and GlcNpS.<sup>[50]</sup>

Finally a 3-*O*-sulfotransferase acts upon the polymer and modifies certain GlcNpS6S residues.<sup>[53]</sup> The 3-*O*-sulfation is required for the anticoagulant activity of heparin, and the pentasaccharide sequence formed by the 3-*O*-sulfotransferase is the minimum structure required for binding antithrombin III. The 3-*O*-sulfotransferase has been cloned and purified and like for many of the other biosynthetic enzymes, there are multiple isoforms having different specificities.<sup>[54]</sup> All the sulfotransferase reactions described above require 3'-phosphoadenosine-5'-phosphosulfate (PAPS) as a sulfate donor.

The apparently random and incomplete nature of the initial *N*-deacetylation is primarily responsible for the introduction

of structural heterogeneity into the polymer at an early stage of biosynthesis. The specificity of this enzyme after its initial modification is also responsible for the block structures seen in heparan sulfate, where there are highly sulfated sequences separated by sequences of nonsulfated disaccharides.<sup>[42, 55]</sup> The overall structural variability of the heparin/heparan sulfate polymer is the result of the incomplete nature of modifications by the biosynthetic enzymes and it is still not clearly understood what additional factors serve as the regulating elements for these enzymes in the biosynthetic pathway.



Scheme 3. Biosynthetic pathway to heparin/heparan sulfate proteoglycans and their degradation to peptidoglycans and glycosaminoglycans. Protein synthesis takes place in the endoplasmic reticulum, linkage synthesis, chain elongation, and modification take place in the golgi, and proteolysis and glucuronidase digestion take place in the granules or lysosomes.

## 2.4. Medical Importance of Heparin

Heparin and LMW heparins are the most commonly used clinical anticoagulants. Heparin is administered intravenously (LMW heparin can be administered either intravenously or subcutaneously, improving its scope of therapeutic applications) during most extracorporeal procedures (where blood is removed from the body and passed through a device) such as kidney dialysis and membrane oxygenation, used in heart bypass procedures.<sup>[56]</sup> The use of these devices, requiring heparinization, can often lead to hemorrhagic complications. Systemic heparinization is also used in the treatment of deep vein thrombosis and in a variety of other surgical procedures.<sup>[57]</sup> Heparin-induced thrombocytopenia (HIT), a complex process which results in loss of platelets, is currently recognized to be one of the most catastrophic complications of heparin treatment.<sup>[58]</sup>

## 3. Interaction of Heparin with Proteins

With the discovery of increasing numbers of heparin-binding proteins there was a need to characterize the

molecular properties, within the proteins and heparin, responsible for specific recognition (Table 1). The first study to look at the general structural requirements for GAG–protein interactions was conducted by Cardin and Weintraub in 1989.<sup>[59]</sup> They compared the heparin-binding domains of four proteins, apolipoprotein B, apolipoprotein E, vitronectin, and platelet factor 4. This study demonstrated that, in addition to sequence similarity, these domains also had defined motifs and were classified into two consensus sequences, XBBXB and XBBBXXB (B is a basic and X a hydrophobic (neutral and hydrophobic) amino acid residue). These consensus sequences were also shown to occur in other proteins known to bind heparin. Molecular modeling studies performed on these consensus sequences showed that their presence in certain secondary structural conformations resulted in the oriented display of the basic residues facilitating their interaction with the negatively charged sulfo groups on heparin. Their results suggested that if the XBBXB sequence were in a  $\beta$ -strand conformation, the basic amino acids would be aligned on one face of the  $\beta$ -strand while the hydrophobic amino acids would point back into the protein core. Similarly, if the XBBBXXB sequence were folded into

Table 1. Characteristics of selected heparin-binding proteins.

| Heparin-binding protein       | Physiological/Pathological role                                      | Characteristics of heparin binding |                      |                                  |                               | Ref.       |
|-------------------------------|----------------------------------------------------------------------|------------------------------------|----------------------|----------------------------------|-------------------------------|------------|
|                               |                                                                      | $K_d$                              | Oligosaccharide size | Sequence features <sup>[d]</sup> | Function                      |            |
| proteases/esterases           |                                                                      |                                    |                      |                                  |                               |            |
| AT III <sup>[a]</sup>         | coagulation cascade serpin                                           | ca. 20 nM                          | 5-mer                | GlcNS6S3S                        | enhances                      | [83, 104]  |
| SLPI                          | inhibits elastase and cathepsin G                                    | ca. 6 nM                           | 12-mer to 14-mer     | IS                               | enhances                      | [76]       |
| C1 INH                        | inhibits C1 esterase                                                 | ca. 100 nM                         | –                    | HS                               | enhances                      | [87]       |
| VCP                           | protects host cell from complement                                   | nM                                 | –                    |                                  | unclear                       | [114, 115] |
| growth factors                |                                                                      |                                    |                      |                                  |                               |            |
| FGF-1 <sup>[a]</sup>          | cell proliferation, differentiation, morphogenesis, and angiogenesis | nM                                 | 4-mer to 6-mer       | IdoA2S-GlcNS6S                   | activates signal transduction | [34, 93]   |
| FGF-2 <sup>[a,b]</sup>        | (same as FGF-1)                                                      | nM                                 | 4-mer to 6-mer       | IdoA2S-GlcNS                     | (same as FGF-1)               | [31, 88]   |
| chemokines                    |                                                                      |                                    |                      |                                  |                               |            |
| PF-4 <sup>[b]</sup>           | inflammation and wound healing                                       | nM                                 | 12-mer               | HS/LS/HS                         | inactivates heparin           | [136, 137] |
| IL-8                          | pro-inflammatory cytokine                                            | ca. 6 $\mu$ M                      | 18-mer to 20-mer     | HS/LS/HS                         | promotes                      | [139]      |
| SDF-1 $\alpha$ <sup>[c]</sup> | pro-inflammatory mediator                                            | ca. 20 nM                          | 12-mer to 14-mer     | HS                               | localizes                     | [142, 143] |
| lipid-binding proteins        |                                                                      |                                    |                      |                                  |                               |            |
| Annexin II                    | receptor for TPA and plasminogen, CMV and tenascin C                 | ca. 30 nM                          | 4-mer to 5-mer       | HS                               | unclear                       | [151]      |
| Annexin V <sup>[a]</sup>      | anticoagulant activity; influenza and hepatitis B viral entry        | ca. 20 nM                          | 8-mer                | HS                               | assembles                     | [85, 157]  |
| ApoE <sup>[b]</sup>           | lipid transport; AD risk factor                                      | ca. 100 nM                         | 8-mer                | HS                               | localizes                     | [166]      |
| pathogen proteins             |                                                                      |                                    |                      |                                  |                               |            |
| HIV-1 gp120                   | viral entry                                                          | 0.3 $\mu$ M                        | 10-mer               | HS                               | inhibits                      | [173, 175] |
| CypA                          | viral localization and entry                                         | –                                  | –                    | –                                | inhibits                      | [177]      |
| Tat                           | transactivating factor, primes cells for HIV infection               | ca. 70 nM                          | 6-mer                | HS                               | antagonizes                   | [181]      |
| HSV gB and gC                 | viral entry into cell                                                | –                                  | –                    | –                                | inhibits                      | [184, 186] |
| HSV gD                        | viral entry and fusion                                               | –                                  | –                    | GlcNH <sub>2</sub> 3S            | inhibits                      | [70]       |
| Dengue virus envelope protein | viral localization                                                   | ca. 15 nM                          | 10-mer               | HS                               | inhibits                      | [187]      |
| Malaria CS protein            | sporozoite attachment to hepatocytes                                 | ca. 40 nM                          | 10-mer               | HS                               | inhibits                      | [193–195]  |
| adhesion proteins             |                                                                      |                                    |                      |                                  |                               |            |
| selectins                     | adhesion, inflammation, and metastasis                               | $\mu$ M                            | $\geq$ 4-mer         | HS with GlcNH <sub>2</sub>       | blocks                        | [205, 206] |
| vitronectin                   | cell adhesion and migration                                          | nM                                 | –                    | –                                | removes                       | [200, 201] |
| fibronectin                   | adhesion and traction                                                | $\mu$ M                            | 8-mer to 14-mer      | HS with GlcNS                    | reorganizes                   | [241]      |
| HB-GAM <sup>[b]</sup>         | neurite outgrowth in development                                     | ca. 10 nM                          | 16-mer to 18-mer     | HS                               | mediates                      | [86, 211]  |
| AP                            | in amyloid plaque                                                    | $\mu$ M                            | 4-mer                | HS                               | assembles                     | [152, 216] |

[a] X-ray cocrystal structure of the oligosaccharide–protein complex available. [b] Solution structure of the oligosaccharide–protein complex available (NMR).

[c] Molecular modeling docking studies of the oligosaccharide–protein complex available. [d] HS: high sulfation, IS: intermediate sulfation, LS: low sulfation.

an  $\alpha$ -helix, then the basic amino acids would be displayed on one side of the helix (Figure 2) with the hydrophobic residues pointing back into the protein core. Using this model, Sobel and coworkers proposed a third consensus sequence, XBBBXXBBBXXBBX, in a heparin-binding protein, the

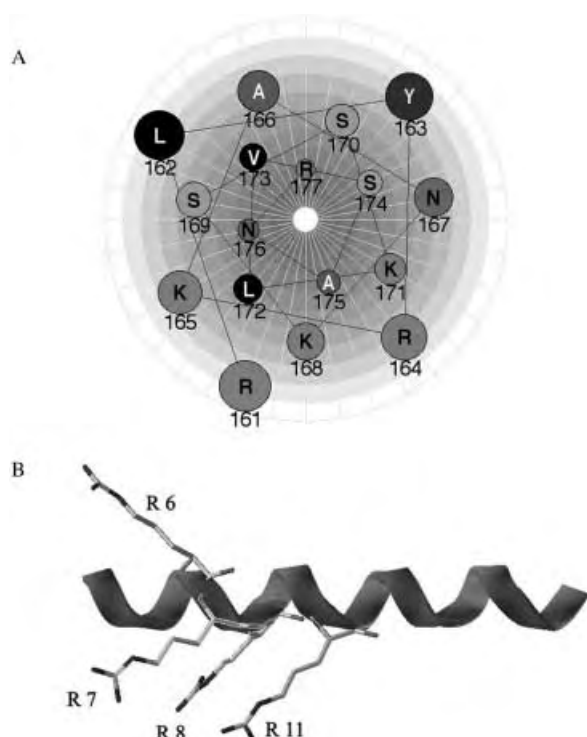


Figure 2. Cardin and Weintraub motifs on an  $\alpha$ -helix display basic residues R and K on one face. A) Helical wheel diagram of apolipoprotein E (residues 161–177). B) Helical model of an XBBBXXBX motif built using the software package SYBYL version 6.3.

von Willebrand factor.<sup>[60]</sup> These motifs serve as initial sequence probes to determine whether a protein can possibly bind heparin. However, with the discovery of more heparin-binding proteins, it was observed that the motif hypothesis did not always hold. Basic residues that are distant in sequence could be closer in the folded state. Thus, spatial orientation of basic residues, rather than sequence proximity, is an important factor in determining heparin binding ability. Margalit and coworkers also used molecular modeling to examine linearly contiguous heparin-binding sites that were shown by others to interact with heparin. In established heparin-binding sites, with known secondary structure, they observed that a distance of approximately 20 Å between basic amino acids is important for interaction, irrespective of whether the heparin-binding site exists as an  $\alpha$ -helix or a  $\beta$ -strand.<sup>[61]</sup> As most of the basic residues were aligned on opposite sides of the secondary structural element, the authors proposed that heparin coils around its binding domain to interact with these positively charged residues. They also suggested that this coiling can induce conformational changes in the heparin-binding protein.

Heparin-binding sites are commonly observed on the external surface of proteins and correspond to shallow pockets of positive charge. Thus, the topology of the

heparin-binding site is also an important factor in heparin-binding consensus sequences. Structural analysis of the heparin-binding sites in acidic fibroblast growth factor (FGF-1), basic FGF (FGF-2), and transforming growth factor  $\beta$ -1 (TGF  $\beta$ -1) implicated a TXXBXXTBXXXTB motif (Figure 3), where T defines a turn, B a basic arginine or lysine residue (or occasionally a hydrogen-bonding glutamine) and

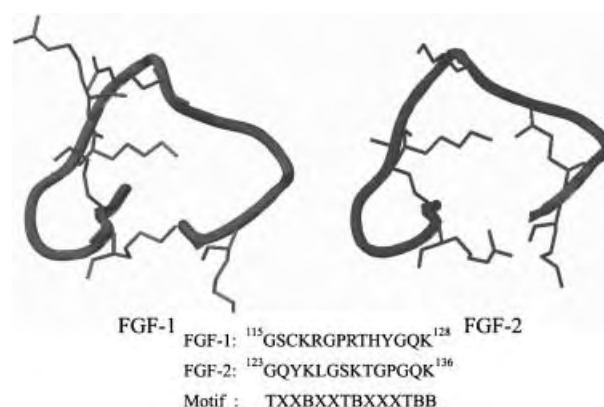


Figure 3. Turn-rich heparin-binding motifs in the FGF protein family. The peptide backbone is a bold line, and only the side chains of the basic residues are displayed.

X a hydrophobic residue.<sup>[62]</sup> The importance of the shape of this binding site in the FGF family was further demonstrated by affinity studies with synthetic linear and cyclic peptides based on a sequence analogous to the heparin-binding site in FGF.<sup>[63]</sup> The cyclic peptide, designed to resemble the structure of the heparin-binding site in FGF, bound more tightly to heparan sulfate than the acyclic peptide of the same sequence or a cyclic peptide containing a D-proline turn. Not all heparin-binding proteins contain linearly contiguous heparin-binding sites. Basic amino acids that are distant in sequence can be brought spatially close through the folding of the protein. This is observed for antithrombin III, where both a linearly contiguous heparin-binding domain and sequence-remote basic amino acids are appropriately positioned to bind heparin.<sup>[64]</sup>

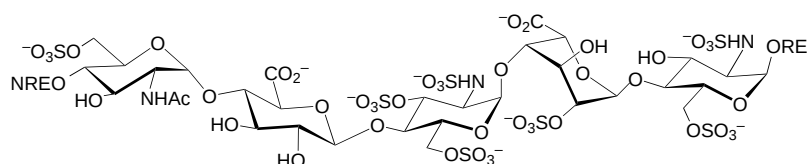
Studies performed in our laboratory looked at the common amino acids in heparin-binding domains in proteins and the importance of spacing of basic amino acids in heparin binding. Using peptide libraries we assessed the affinity of randomly synthesized heptamers for both heparin and heparan sulfate. Peptides enriched in arginine and lysine, but not histidine, bound with greatest affinity. Peptides with high affinity for heparin and heparan sulfate were also enriched in other polar amino acids including serine.<sup>[65]</sup> It was also observed that known heparin-binding domains contain amino acids (asparagine and glutamine) capable of hydrogen bonding. The relative strengths of heparin binding by basic amino acid residues was compared and arginine was shown to bind 2.5 times more tightly than lysine. The tight interaction observed for arginine appears to result from strong hydrogen bonding between the guanidino group of arginine and a sulfo group in heparin.<sup>[66]</sup>

The effect of the pattern and spacing of the basic amino acids in heparin-binding sites was also studied using a series of synthetic peptides.<sup>[67]</sup> The relative binding affinities of two peptide series, -RRG<sub>m</sub>RR- and -RRRG<sub>m</sub>R- (R is arginine and G glycine) was examined. Heparin interacted most tightly with peptides containing a complementary binding site of high positive charge density while less sulfated heparan sulfate interacted most tightly with a complementary site on a peptide that had more widely spaced basic residues. Thus, the results of this study are entirely consistent with our understanding of heparin and heparan sulfate structures.

### 3.1. Protein-Binding Motifs within Heparin and Heparan Sulfate

Specific recognition between heparin and proteins also requires defined sequences within the heparin chain. Heparin and heparan sulfate predominantly exhibit linear helical secondary structures with sulfo and carboxyl groups displayed at defined intervals and in defined orientations along the polysaccharide backbone. A heparin-binding domain on a protein would, therefore, require a minimum number of saccharide residues within the heparin chain to appropriately display these charged groups to facilitate a tight and specific interaction.

The first example of a defined protein-binding motif within heparin was the discovery of a discrete pentasaccharide sequence required for binding antithrombin III.<sup>[10]</sup> This pentasaccharide sequence is rare, occurring in only about one-third of the chains in heparin. Its most distinguishing feature is the unusual 3-*O*-sulfo group on an internal GlcNpS6S residue (Scheme 4), which is absolutely essential for its high affinity to



Scheme 4. Structure of the AT-III-binding pentasaccharide sequence in heparin.

antithrombin III.<sup>[68]</sup> The 3-*O*-sulfation reaction is the final step in heparin and heparan sulfate biosynthesis and there are multiple 3-*O*-sulfotransferase isoforms having different substrate specificities. The treatment of a biochip-immobilized heparan sulfate, that has a low affinity for AT III, with one of these isoforms affords a structurally modified high affinity chain.<sup>[69]</sup> A heparan sulfate modified at specific glucosamine residues by a second of these 3-*O*-sulfotransferase isoforms offers sites for the binding of the viral envelope glycoprotein of herpes simplex virus type 1 (HSV-1).<sup>[70]</sup> This binding is postulated to be important in the initiation of HSV-1 entry into cells. The 3-*O*-sulfo group in heparan sulfate is also believed to be important for the specific interaction with fibroblast growth factor 7 (FGF-7).<sup>[71]</sup> Another study suggests that the antithrombin-binding motif within heparan sulfate is required for the formation of a functional complex with the FGF receptor kinase ectodomain.<sup>[72]</sup>

The proteins of the FGF family are probably the most extensively studied heparin-binding proteins. X-ray crystallography data on FGF-1<sup>[34]</sup> and FGF-2<sup>[31]</sup> complexes with heparin oligosaccharides have been useful in defining the precise groups within heparin that are important for these biologically significant interactions. Both structural and experimental data suggest that the 6-*O*-sulfo groups within heparin, while not directly important in the binding of FGF-2 to heparin,<sup>[73]</sup> are apparently required for the mitogenic activity of FGF-2.<sup>[74]</sup> In contrast, the interaction of FGF-1 with heparin is directly mediated through contacts with the 6-*O*-sulfo groups on heparin. These differences suggest a specificity of interaction for various members of the same family of growth factors.<sup>[75]</sup> While the interaction between proteins and heparin is primarily ionic and based on the presence and appropriate positioning of sulfo and carboxyl groups, this may not always be the case. For example, it has been observed that in the interaction between secretory leukocyte protease inhibitor (SLPI) and heparin, undersulfated heparin oligosaccharide sequences are required for specific high affinity interaction, suggesting the importance of hydrogen-bonding interactions through the hydroxyl groups present in heparin.<sup>[76]</sup>

### 3.2. Types of Interactions

Clearly the most prominent type of interaction between heparin and a protein is ionic. Clusters of positively charged basic amino acids on proteins form ion pairs with spatially defined negatively charged sulfo or carboxyl groups on the heparin chain. However, in some cases there is a significant contribution to the binding by nonionic interactions such as

hydrogen bonding. Isothermal titration calorimetry (ITC) studies of the interaction of brain natriuretic peptide (BNP) with heparin revealed that only a small portion of the free energy of this interaction resulted from ionic contributions. The major contribution was from hydrogen bonding between the polar amino acids on BNP and heparin.<sup>[77]</sup> Hydrophobic forces may also play a minor role in

heparin–protein interactions. Based on NMR data, Bae and coworkers suggested the importance of a tyrosine residue in a synthetic antithrombin III peptide in an apparently specific, hydrophobic interaction with the *N*-acetyl group in the AT-III-binding pentasaccharide sequence in porcine mucosal heparin.<sup>[78]</sup>

### 3.3. Kinetics, Thermodynamics, and Measurement of Heparin–Protein Interactions

Heparin resembles DNA as both are highly charged linear polymers that behave as polyelectrolytes. The high repulsive energy of multiple negatively charged groups in these polyelectrolytes promotes cation (i.e., Na<sup>+</sup>) binding to minimize these forces.<sup>[79]</sup> The binding of Na<sup>+</sup> ions by a polyelectrolyte is entropically unfavorable. When a polyelectrolyte such as



heparin binds a protein, the positively charged amino acid residues on the protein interact at anionic sites resulting in the entropically favorable release of  $\text{Na}^+$  ions. Thus, much of the free energy of interaction of heparin with proteins is derived from the entropically favorable release of  $\text{Na}^+$  ions, and this is called the “polyelectrolyte effect”.<sup>[80]</sup> The free energy of interaction, which is related to the observed dissociation constant ( $K_d$ ), has contributions from the polyelectrolyte effect, hydrogen bonding, and hydrophobic interactions.<sup>[81]</sup> Specifically,  $K_d$  is related to both ionic and nonionic contributions according to Equation (1) where  $K_{d,\text{nonionic}}$  is the dissociation constant in the absence of the polyelectrolyte effect,  $m$  is the number of  $\text{Na}^+$  ions released on heparin–protein binding, and  $f$  is a small fraction of anionic charge on the polyelectrolyte that is not charge-neutralized by  $\text{Na}^+$  ions. Binding measurements at a salt concentration of 1M reflect the nonpolyelectrolyte contribution to the binding since  $\lg K_d = \lg K_{d,\text{nonionic}}$ . At physiologic salt concentrations the polyelectrolyte effect plays a significant role on heparin binding to proteins.<sup>[82]</sup>

$$\lg K_d = \lg K_{d,\text{nonionic}} + m(1-f)\lg[\text{Na}^+] \quad (1)$$

The kinetics of interaction for heparin binding to antithrombin III have been extensively studied.<sup>[83]</sup> Since AT III undergoes a conformational change on binding heparin,<sup>[84]</sup> and this process can be monitored by a change in AT III fluorescence, it represents a good system to study by stopped-flow fluorimetry. For most other heparin-binding proteins, where there is no such observable change following the binding event, it is very difficult to study the kinetics of the interaction. However, the development of surface plasmon resonance (SPR), which allows binding events to be measured in real time, has made it possible to study the kinetics of heparin–protein interactions.<sup>[85–87]</sup>

Various methods are utilized in studying the binding affinity of heparin with proteins. In affinity chromatography, the most commonly used technique, heparin or the heparin-binding protein is immobilized on a solid matrix and its binding partner is applied to the column. The binding partner is then released with salt and the amount required for elution is a quantitative measure of the ionic component of the binding affinity. This approach fails to measure the hydrophobic and hydrogen-bonding contributions to binding. Affinity chromatography is difficult to use in studying interactions dependent on divalent cations<sup>[85]</sup> and requires the immobilization of one of the binding partners. ITC provides information on the thermodynamics of heparin–protein interactions (Figure 4).<sup>[88]</sup> In this technique, one of the interacting species is placed in solution in a thermostatted cell and the other species is injected into this cell. The heat released on binding following each injection is measured, affording a sigmoidal titration curve. By fitting this curve, values for the enthalpy ( $\Delta H$ ), the association constant ( $K_a$ ), and the binding stoichiometry ( $n$ ) are obtained. ITC typically requires milligram amounts of each interacting species, is useful only in measuring association constants in the range  $10^4$  to  $10^8$ , and involves relatively high concentrations of interacting species often leading to precipitation.

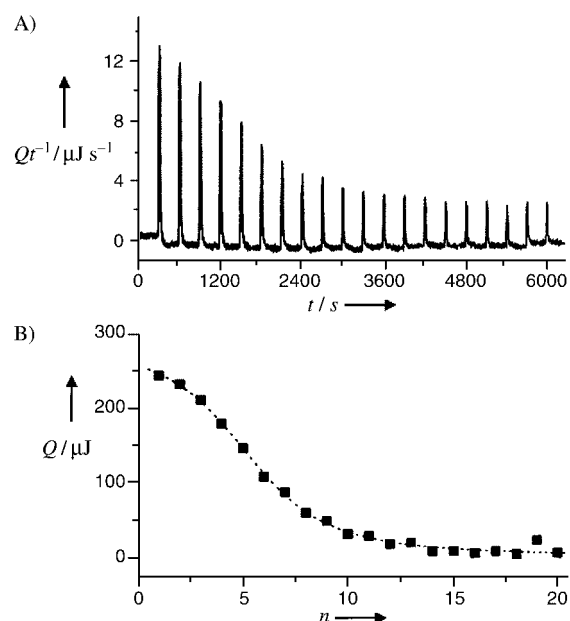


Figure 4. Data obtained from an ITC experiment with heparin and BNP. A) Raw data showing the heat released on binding in  $\mu\text{J s}^{-1}$  ( $Qr^{-1}$ ) with each injection. B) Fitted heats of interaction, giving a sigmoidal binding curve. The heat released ( $Q$ ) is plotted against the number of injections ( $n$ ).

NMR spectroscopy can afford extremely valuable information about heparin–protein interactions.<sup>[78]</sup> NMR analysis provides primarily structural and conformational data that are useful in identifying the precise contact points between interacting molecules. While NMR experiments give a relatively detailed picture of the interaction between heparin and protein, the insensitivity of this method requires milligram quantities of interacting species at high concentrations, raising solubility problems and making it difficult to accurately determine the association constant ( $K_a$ ).

Fluorescence spectroscopy is a very sensitive method that can provide a wealth of information about heparin–protein interactions on very small amounts of sample. Conformational changes in the protein, which often occur on heparin binding, can be measured through changes in the environment of intrinsic fluorophores such as tyrosine and tryptophan.<sup>[78]</sup> The association constant can be obtained by monitoring the change in fluorescence as one interacting species is titrated into a solution of the other. This technique is limited to protein–heparin binding that results in a change in fluorescence. Fluorescence resonance energy transfer (FRET) between an intrinsic fluorophore in the protein and an extrinsic fluorophore in heparin (fluorescently labeled heparin) can afford both  $K_a$  and information on the distance between the two fluorophores of up to 80 Å.<sup>[89]</sup> One concern associated with this approach is that derivatizing heparin (or particularly a small oligosaccharide) with an extrinsic fluorophore can perturb both its conformation and its interaction with the protein.

Surface plasmon resonance (SPR) is a powerful technique for studying interactions. Here one of the interacting species is immobilized on the surface of a chip and the binding partner is flowed over this chip. The resulting interaction changes the refractive index of the chip, which is measured as a change in

the intensity and angle of light reflected from the chip's surface. The magnitude of this change is directly proportional to the mass of the binding partner being bound, affording a real-time measurement of association and dissociation rates from which the dissociation constant can be calculated (Figure 5).<sup>[85, 86]</sup> Signals are easily obtained from sub-microgram quantities of material. While this technique can provide important information on binding kinetics, it suffers from potential experimental artifacts that arise from ligand immobilization.

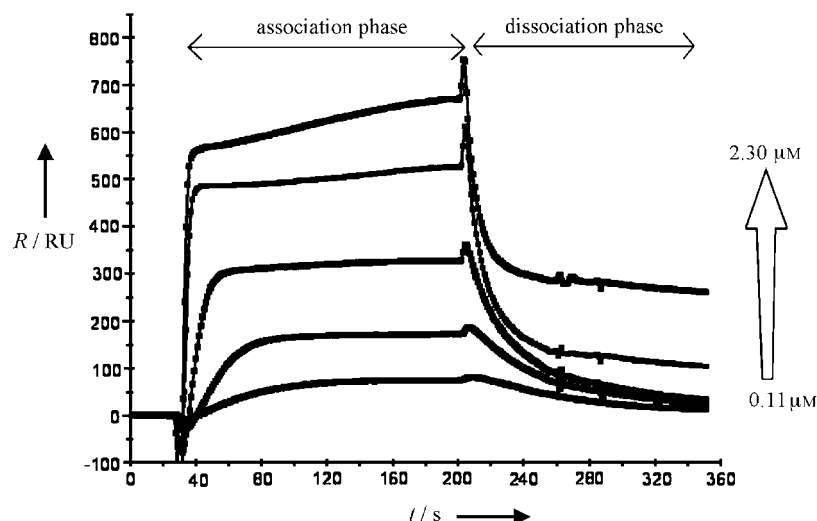


Figure 5. SPR sensorgram data obtained for the interaction of the apoE4 N-terminal domain with heparin. Solutions with varying concentrations (0.11–2.30  $\mu\text{M}$ ) of the apoE4 domain were flowed over heparin immobilized on a chip. The change in surface response ( $R$ ) over time ( $t$ ) is plotted. RU = response unit.

Other techniques that can be used to study heparin–protein interactions include affinity coelectrophoresis (ACE),<sup>[90]</sup> two-dimensional affinity resolution electrophoresis (2-DARE),<sup>[91]</sup> equilibrium dialysis,<sup>[66]</sup> competitive binding techniques,<sup>[92]</sup> analytical centrifugation,<sup>[93]</sup> and circular dichroism.<sup>[94]</sup> X-ray crystallography of heparin oligosaccharides in complexes with proteins provides high-resolution structural information,<sup>[31, 34]</sup> but requires large quantities of homogeneous interacting species.

### 3.4. Modeling Studies on Heparin–Protein Interactions

Molecular modeling can provide useful information on molecular interactions but its predictive power still needs to be substantiated. The value of modeling is that intricate dynamic details of molecular level events can be visualized with a relatively small investment of time and cost. One of the problems of molecular mechanics and dynamics is the limited availability of reliable potential energy functions, particularly for molecules containing functionality such as *N*- and *O*-sulfo groups. Modeling protocols and reliable potential energy functions for studying proteins and DNA are well established and many empirical forcefields such as AMBER, CHARMM, MM2, and TRIPOS are widely used.

Modeling of heparin initially required the derivation of potential energy functions, using ab initio calculations, of the *N*- and *O*-sulfo groups attached to 2-, 3-, and 6-positions of the pyranosyl units.<sup>[95]</sup> The development of efficient modeling protocols for understanding the steric and spatial considerations of oligosaccharides is also important in studying heparin–protein interactions.<sup>[96]</sup> The NMR structure of a heparin dodecasaccharide (Figure 1)<sup>[23]</sup> and the high-resolution X-ray crystallographic structures of heparin oligosaccharides<sup>[31, 34]</sup> provided an important starting point for modeling heparin–protein interactions. Docking studies with heparin oligosaccharides and their protein-binding partners can afford additional structural information on the interaction. However, such studies present a challenge because of the weak surface complementarity, the high charge density of heparin and the heparin-binding site, and the highly flexible nature of the heparin chain.

Docking studies have been carried out between the heparin-binding peptide sequences of antithrombin III and the AT-III-binding pentasaccharide sequence to study the structure–activity relationship (SAR) of this interaction.<sup>[97]</sup> In a recent study, several docking protocols for the prediction of heparin-binding sites on AT III, FGF-1, and FGF-2 were tested and compared to crystallographic data available for these proteins in complexes with their oligosaccharide binding partners. A global search for likely binding sites was initially performed using sulfated monosaccharides and disaccharides, followed by a local docking of a hexasaccharide. After correctly predicting the binding site for the test molecules, these protocols were used to predict the heparin-binding site on interleukin-8 (IL-8), a chemokine with a central role in immune response.<sup>[98]</sup> This strategy significantly reduces the required computational time compared to a global docking of the hexasaccharide.

## 4. Regulation of Proteases and Esterases

The interaction of heparin with antithrombin III is the first well-studied example of a heparin–protein interaction. Heparin is believed to function as an anticoagulant primarily through its interaction with AT III by enhancing AT-III-mediated inhibition of blood coagulation factors, including thrombin and factor Xa. These coagulation factors are serine proteases with trypsin-like specificity for arginyl linkages. AT III is a member of the serpin (*serine protease inhibitor*) superfamily of proteins that includes more than 40 proteins.<sup>[99]</sup> The serpins react with serine proteases to form inactive complexes, which are then cleared from the circulation. All the coagulation factors (with the exception of factor VIIa) are inhibited by AT III, forming a covalent 1:1 complex with these enzymes. The inactivation of these proteases by AT III is greatly accelerated by the binding of heparin. Heparin binds to AT III and thrombin in a ternary complex, increasing the

bimolecular rate constant for the inhibition of thrombin by a factor of 2000.<sup>[9]</sup> The interaction of heparin with AT III and serine proteases proceeds through several stages. Initial heparin binding to AT III is a low-affinity interaction mediated by a well-defined unique pentasaccharide sequence within heparin. This binding causes a conformational change<sup>[84]</sup> in the structure of AT III, which promotes additional interactions between AT III and heparin, resulting in a stronger binding. The conformational change also leads to the expulsion of a loop with a protease-reactive site in AT III that facilitates the reaction of the target protease with AT III yielding a cleaved and conformationally altered AT III covalently bound to the active site of the serine protease as an acyl–enzyme intermediate. As a result of the cleavage, the affinity of AT III for heparin is markedly diminished,<sup>[100]</sup> causing heparin to dissociate in an unaltered form, free to catalyze further reactions between AT III and its target serine proteases. The acyl–enzyme intermediate then dissociates very slowly ( $t_{1/2} \sim 5$  days) to yield the unaltered serine protease and the cleaved antithrombin, which is no longer an active serpin and has lost its heparin binding affinity.<sup>[101]</sup>

Heparin chains at least 16 saccharides in length are required to accelerate the reaction of antithrombin with thrombin, even though only the pentasaccharide sequence is necessary to bind AT III.<sup>[102]</sup> In contrast, heparin chains as small as the AT-III-binding pentasaccharide are able to accelerate the inactivation of the other target coagulation enzymes, such as Factor Xa.<sup>[103]</sup> Heparin binding to AT III induces a conformational change, resulting in a 40% enhancement of AT III fluorescence, thus facilitating kinetic studies that rely on stopped-flow fluorimetry.<sup>[83]</sup> The X-ray crystal structure of an AT-III–pentasaccharide complex was used to identify residues in AT III involved in this interaction as well as important functional groups within the pentasaccharide (Figure 6).<sup>[104]</sup> The residues important in the interaction have been altered through site-directed mutagenesis and stopped-flow kinetic studies were carried out to assess the relative contributions of these residues to binding.<sup>[105]</sup> The role of individual saccharide residues of the heparin pentasaccharide in the allosteric activation of AT III has also been determined by studying the effect of truncating pentasaccharide residues, at either its reducing or nonreducing end, on oligosaccharide binding and the induction of a conformational change in AT III.<sup>[106]</sup> These studies established that the three saccharide residues on the nonreducing end of the pentasaccharide sequence are capable of fully activating AT III. While the reducing-end residues are not essential for this activation, they stabilize the activated conformation. Detailed characterization of the determinants involved in this physiologically relevant interaction is important, as it would enable the development of more specific heparin analogues that might retain anticoagulant activity without the undesirable side effects observed with heparin.

Heparin is principally located in the granules of tissue mast cells that are closely associated with the immune response. Thus, the ability of heparin to regulate the major activities of the complement cascade is an area of active interest.<sup>[107]</sup> The complement system consists of about 20 plasma proteins that interact in two related sets of reactions: the antibody-dependent classical pathway and the antibody-independent



Figure 6. Structure of a synthetic AT-III-binding pentasaccharide in its complex with antithrombin III. The protein is shown as a green ribbon and the pentasaccharide as a space-filling model with sulfur atoms in yellow and oxygen atoms in red.

alternative pathway. Both pathways consist of the sequential activation of a series of serine esterases, much like in the blood coagulation pathway. Studies indicate the importance of *O*-sulfo groups in heparin and a minimum oligosaccharide size for complement regulation.<sup>[108]</sup> The classical pathway is initiated when complement protein C1 esterase, also called the recognition unit, specifically binds to a cell surface antigen–antibody aggregate. C1 esterase is regulated by a natural inhibitor present in serum, called C1 esterase inhibitor (C1INH).<sup>[109]</sup> Heparin and other glycosaminoglycans augment the activity of C1INH on C1 components in vitro.<sup>[110]</sup> The ability of heparin and heparan sulfate to bind C1INH and enhance its inhibitory activity has been studied using surface plasmon resonance and in vitro assays.<sup>[87]</sup> Heparin immobilized on a biosensor chip interacted with C1INH ( $K_d \approx 100$  nM), while no binding between heparan sulfate and C1INH was observed. In vitro assays indicated that heparin, and to a slightly greater extent LMW heparin, augmented the activity of C1INH on cell-bound C1 and the order of the reaction suggested the involvement of a ternary complex in which cell-bound C1 interacts with both heparin and C1INH. Heparin is also believed to directly bind to and inhibit C1 activity. There is evidence to suggest that C1 recognizes the fraction of heparin with high antithrombin III affinity.<sup>[111]</sup> Heparin also has a profound effect on the complement cascade through its interaction with a number of other complement proteins.<sup>[108]</sup>

Chemically modified, N-acetylated heparin inhibits cobra venom factor activation of the complement cascade in vivo.<sup>[112]</sup> Vaccinia virus complement control protein (VCP) is secreted from virally infected cells and is believed to protect

the host cell from complement attack prior to the release of viral progeny.<sup>[113]</sup> VCP inhibits both pathways of complement activation by binding the third and fourth complement components. VCP, a heparin-binding protein, may bind heparan sulfate PGs on the surface of human endothelial cells.<sup>[114]</sup> A recent crystal structure analysis of VCP revealed a putative heparin-binding site at its C-terminus and experiments indicate that VCP can bind heparin and control complement activation simultaneously.<sup>[115]</sup>

## 5. Interaction of Heparin with Extracellular Signaling Molecules

### 5.1. Interaction of Heparin with Growth Factors

Fibroblast growth factors (FGFs) are members of a large family of proteins that are involved in developmental and physiological processes including cell proliferation, differentiation, morphogenesis, and angiogenesis (currently 21 members).<sup>[116]</sup> FGFs are heparin-binding proteins that have a high affinity for cell surface heparan sulfate proteoglycans. With the possible exception of antithrombin III, no heparin-binding proteins have been more thoroughly studied. Vertebrate FGFs have an internal core region of 28 highly conserved and six invariant amino acids and range in molecular weight from 17 to 34 kDa.<sup>[117]</sup>

Acidic fibroblast growth factor (FGF-1) and basic fibroblast growth factor (FGF-2) were the first members of the family to be discovered, and the thermodynamics and kinetics of their interaction with heparin have been extensively studied.<sup>[88, 93]</sup> High-resolution X-ray crystallographic data on these proteins in complexes with heparin oligosaccharides have been published.<sup>[31, 34]</sup> These growth factors exert their biological effects by binding to different, specific cell surface receptors called fibroblast growth factor receptors (FGFR-1 – FGFR-4). The FGFRs are transmembrane tyrosine kinase receptors expressed as multiple splice variants with different affinities for the different FGFs.<sup>[75]</sup> The FGFRs are also heparin-binding proteins,<sup>[118]</sup> thus, the three compounds FGF, FGFR, and heparan sulfate must interact simultaneously to initiate signal transduction.<sup>[119]</sup> FGF-stimulated signal transduction is similar to other receptor-mediated pathways in that it involves the dimerization of the FGFRs. Cell membrane heparan sulfate binds multiple FGF molecules promoting FGFR dimerization and signal transduction. High-resolution X-ray crystal structures of complexes of FGF, FGFR, and a heparin oligosaccharide provide an insight into the stoichiometry and structural aspects of this physiologically relevant interaction (Figure 7).<sup>[120, 121]</sup>

The first study reports the crystal structure of a dimeric ternary complex of FGF-2, FGFR-1, and a heparin deca-saccharide (2:2:2) at a resolution of 3 Å.<sup>[120]</sup> In each FGF – FGFR 1:1 complex, heparin makes numerous contacts with both FGF-2 and FGFR-1 stabilizing FGF – FGFR binding. Heparin also makes contacts with the FGFR-1 of the adjacent FGF – FGFR complex, thus seeming to promote FGFR dimerization. The heparin binding mode in this structure is not in accordance with previous findings on the minimal

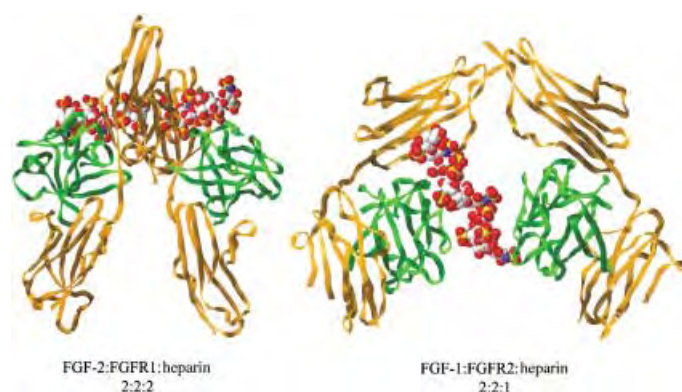


Figure 7. Structures of the recently solved FGF – FGFR – heparin complexes. The FGFR is shown as a gold and the FGF as a green ribbon. The heparin oligosaccharides are shown as space-filling models with sulfur (yellow), oxygen (red) and nitrogen atoms (blue).

heparin chain length sufficient to promote dimerization,<sup>[122]</sup> requiring additional biochemical studies to support these observations. Based on biochemical and crystallographic data, a model can be built in which heparin interacts through its nonreducing end with both FGF-2 and FGFR-1 resulting in the formation of a stable 1:1:1 complex of FGF, FGFR, and heparin. This complex can combine with another 1:1:1 complex through direct FGFR – FGFR contacts, secondary interactions between FGF-2 in one ternary complex and FGFR-1 in the adjacent ternary complex, and indirect heparin-mediated FGFR – FGFR contacts.

The second study reports the crystal structure of a 2:2:1 complex of FGF-1, FGFR-2, and a heparin deca-saccharide at a resolution of 2.8 Å.<sup>[121]</sup> In this case the complex is assembled around a central heparin molecule that links two FGF-1 ligands into a dimer, similar to a previously proposed model.<sup>[34]</sup> There are significant differences in these models with respect to the relative orientation of FGF-1 and heparin. The 2:1 FGF-1 – heparin complex acts as a bridge between the two FGFR-2 molecules. The asymmetric heparin chain in this structure contacts only one receptor molecule. The role of heparan sulfate in this type of receptor dimerization also appears critical, as there are very few protein – protein contacts between the two halves of the pentameric complex.

While both these studies provide important information on the organization of these complexes, there are significant differences in the two structures possibly indicating that different members of the FGF family of ligands and their respective receptors may interact differently with heparan sulfate chains. These differences could result from differences in the distribution and structure of heparan sulfate PGs and FGF receptors on cell surfaces in different tissues.

The vascular endothelial growth factor (VEGF) is an angiogenic factor consisting of four alternatively spliced forms, three of which interact with heparin.<sup>[123]</sup> The hepatocyte growth factor (HGF) binds heparan sulfate to act as a tumor suppressor, morphogen, and angiogenic factor.<sup>[124]</sup> Heparin can also modulate the biological activity of the transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). This factor plays an important role in cell migration and proliferation, extracellular matrix synthesis, and is also involved in immune

processes.<sup>[125]</sup> Other heparin-binding growth factors include the platelet derived growth factor (PDGF) and the heparin-binding epidermal growth factor (HB-EGF).<sup>[126]</sup> In summary, heparan sulfate PGs localize growth factors at the cell surface or in the extracellular matrix and promote their biological activities.

## 5.2. Interaction of Heparin with Chemokines

Chemokines are a group of small, cytokinelike proteins with a variety of biological functions including selective recruitment and activation of cells during inflammation.<sup>[127]</sup> Chemokines also stimulate leukocyte degranulation and promote angiogenesis or angiostasis.<sup>[128]</sup> The first member of the chemokine family to be discovered was the platelet factor 4 (PF-4, now called CXC chemokine ligand 4 or CXCL4). Chemokines were not recognized as chemotactic molecules until the characterization of interleukin 8 (IL-8, now called CXCL8).<sup>[129]</sup> The more than 40 currently identified chemokines can be classified according to the distribution of cysteine residues near the NH<sub>2</sub>-terminus into four major families: CXC, CC, C, and CX<sub>3</sub>C.<sup>[130]</sup> The interaction of chemokines with specific cell populations is mediated by G-protein-coupled receptors having seven transmembrane domains. Chemokine receptors are also believed to play an important role in breast cancer metastasis<sup>[131]</sup> and in the entry of HIV-1 into cells.<sup>[132]</sup> Chemokines can also bind heparin and cell surface GAGs at the vascular endothelium or in the extracellular matrix. This interaction has been suggested to play a role in the formation of haptotactic gradients on the surface of endothelial cells<sup>[133]</sup> and to enhance the local concentration of chemokines in the vicinity of G-protein-coupled receptors.<sup>[134]</sup>

PF-4 is released from platelets and is believed to have a number of properties associated with inflammation and wound healing that are thought to be due to its ability to neutralize the activities of heparin and heparan sulfate proteoglycans. When therapeutically administered heparin binds to PF-4, it can lead to a dangerous immunologically induced loss of platelets causing a condition called heparin-induced thrombocytopenia (HIT). PF-4 exists mainly as a tetramer under physiological conditions and binds to heparin and heparan sulfate with a very high affinity in a 1:1 ratio.<sup>[135]</sup> NMR studies on the interaction of a heparin dodecasaccharide chain with PF-4 suggest that residues in the Arg20–Arg22 loop are involved in heparin binding.<sup>[136]</sup> These studies also indicate that, for certain PF-4:heparin ratios, the heparin chain induces PF-4 to undergo a conformational transition to a partially folded, molten-globule state. The ratio at which this conformational transition occurs is the same ratio at which HIT antibody binding is observed, suggesting that the HIT antibody recognizes a less folded, lower aggregate state of the protein (Figure 8). Another study that looked at the interaction of heparan sulfate with PF-4 identified a large heparan sulfate oligosaccharide that was involved in binding the PF-4 tetramer.<sup>[137]</sup> The authors of this study propose that this oligosaccharide chain is capable of wrapping around the PF-4 molecule, contacting the positively charged residues involved

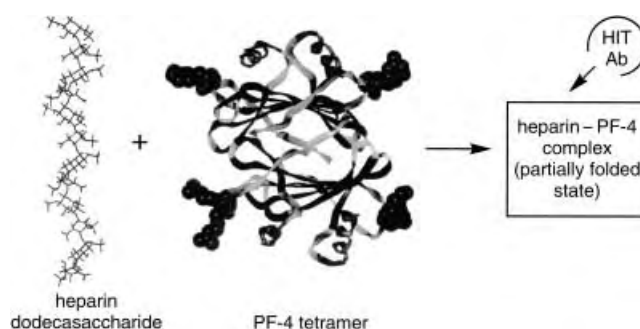


Figure 8. Scheme showing the events leading to HIT. The side chains of the residues involved in heparin binding (Arg20 and Arg22) are shown as space-filling models in the ribbon structure of the PF-4 tetramer.

in the interaction on all four monomers. The 2-*O*-sulfo-iduronate residues in this oligosaccharide were identified to be important for binding to PF-4. Basic residues in the circular array of charges found on the surface of PF-4 are conserved within the family of CXC type chemokines, including IL-8.<sup>[138]</sup> Studies on the interaction of IL-8 with heparan sulfate suggest that a chain length of about 20 saccharide residues is essential for binding with a binding mode in which the heparan sulfate chain binds in a horseshoe fashion to the dimeric protein.<sup>[139]</sup>

The stromal cell derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) is another member of the CXC chemokine family. It is a pro-inflammatory mediator, a potent chemo-attractant for a variety of cells, like monocytes and T-cells, and also a potent inhibitor of the cellular entry of HIV.<sup>[140]</sup> Studies have shown that heparan sulfate is involved in the binding and localizing of SDF-1 $\alpha$  to the cell surface.<sup>[141]</sup> Site-directed mutation studies on SDF-1 $\alpha$  have identified several residues in the protein important for this interaction.<sup>[142]</sup> Molecular docking studies suggest that a heparin dodecasaccharide or tetradecasaccharide is required for binding to SDF-1 $\alpha$ .<sup>[143]</sup> These large binding sites in PF-4, IL-8, and SDF-1 $\alpha$  may be the result of chemokine oligomerization. A heparin-binding consensus motif of the type BBXB is also identified as being important for the interaction. This motif is also implicated as the principle site for heparin binding in a chemokine from the CC family called RANTES (regulated on secretion, normal T-cell expressed and secreted).<sup>[144]</sup> Other members in this family include monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory peptides-1 (MIP-1). Studies have shown that all these chemokines also bind to heparin although with varying affinity and specificity.<sup>[145]</sup> Due to the low circulating concentrations of these chemokines, heparan sulfate PGs may play an important role in sequestering these molecules on the cell surface, thus increasing their effective concentration in the vicinity of their low-affinity receptor sites.<sup>[146]</sup> Data also suggest that cell surface heparan sulfate PGs play a different role than free glycosaminoglycans. Soluble glycosaminoglycans can complex with chemokines in solution and prevent their binding to the receptor, inhibiting downstream receptor-mediated cell responses.<sup>[145]</sup>

The recently identified C chemokine family and the CX<sub>3</sub>C family including lymphotactin and fractalkine<sup>[147]</sup> appear to bind heparin, but the *in vivo* role of this interaction is not well understood. Thus, heparin–chemokine binding appears to be



involved in the regulation of a number of different important physiological processes.

## 6. Interaction of Heparin with Lipid- or Membrane-Binding Proteins

The interaction of heparin with proteins such as antithrombin III and the fibroblast growth factors has been very well studied and characterized in terms of both structural and functional aspects. While there is extensive literature on the interaction of heparin with various families of proteins, less is known about heparin interaction with lipid- or membrane-binding proteins.

Annexins are a family of homologous proteins (currently with 32 members) that are widely distributed and are ubiquitous in eukaryotes.<sup>[148]</sup> A distinctive feature of annexins is their calcium-dependent binding to the surface of phospholipid membranes. Annexins have been implicated in a wide range of functions in eukaryotes, including roles in cell signaling, membrane trafficking, blood coagulation, and inflammation.<sup>[149]</sup> Although annexins are found primarily within cells and lack signal sequences, many extracellular events are now proposed to be annexin-mediated.<sup>[150]</sup> Calcium-dependent glycosaminoglycan binding to annexins has been reported and characterized in several in vitro studies.<sup>[85, 151]</sup> While there are currently over 100 proteins that bind heparin,<sup>[11]</sup> few of these interactions are calcium-dependent: certain annexins, the serum amyloid P component (SAP)<sup>[152]</sup> and P- and L-selectins.<sup>[153]</sup> A qualitative study that examined the glycosaminoglycan-binding properties of annexins IV, V, and VI revealed different binding specificities for these molecules.<sup>[154]</sup>

The extracellular function of annexin V has been extensively studied: it has a role in the entry of and in the infection by influenza and hepatitis B viruses.<sup>[155]</sup> Annexin V also exhibits potent in vitro anticoagulant activity through a proposed mechanism in which it coats placental endothelial cells to form a protective anti-thrombotic shield.<sup>[156]</sup> Kinetic and thermodynamic studies of annexin V demonstrate that its calcium-dependent interaction with heparin and heparan sulfate involves an oligosaccharide sequence of 6–8 saccharide residues.<sup>[85]</sup> Molecular modeling suggests three possible domains within annexin V that could be involved in heparin binding, one on the lipid-binding surface of annexin V and the other two on the exposed surface. A crystal structure analysis of annexin V with bound heparin-derived tetrasaccharides at a resolution of 1.9 Å<sup>[157]</sup> gave the first structural information on the essential role of calcium ions in a heparin–protein interaction (Figure 9). The contact between heparin residues and calcium is indirect and involves shared hydrogen bonds with water molecules near the calcium coordination sites. The calcium dependence of the annexin–heparin interaction arises primarily through inducing the requisite conformation for heparin binding. The structure is characterized by distinct heparin-binding sites situated on opposite surfaces of the protein. Residues important for the interaction can be identified in the crystal structure, in previous modeling studies and from biochemical studies on site-directed mutants.

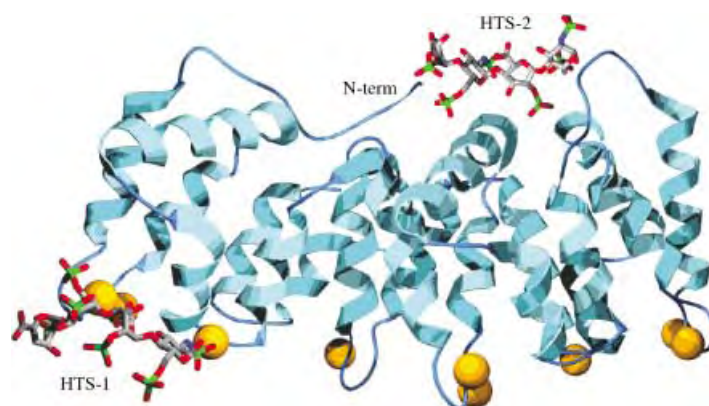


Figure 9. In an annexin V complex two heparin tetrasaccharides are bound on opposite faces of the annexin V molecule. Annexin V is shown as an aqua line and ribbon structure, calcium atoms in gold, and the heparin tetrasaccharides with oxygen (red), sulfur (green), and nitrogen atoms (blue).

Based on all of these data, a model is proposed by which cell surface heparan sulfate PG wraps around the annexin V molecule making contact with all three of its heparin-binding domains (Figure 10 A). The annexin V molecule is then delivered and assembled into an antithrombotic array on the cell surface phospholipid membrane.

Apolipoprotein E (apoE) is an important lipid transport protein in human plasma and brain. Biochemical, cell biological, and epidemiological studies have suggested that apoE is a major genetic risk factor in a number of diseases.<sup>[158]</sup> The human *APOE* gene has three common alleles ( $\epsilon$ 2,  $\epsilon$ 3, and  $\epsilon$ 4). The three isoforms differ at amino acids 112 and 158 and vary in their metabolic properties and association with disease. ApoE4 (Arg112, Arg158) is associated with a higher risk of heart disease<sup>[159]</sup> and is a major genetic risk factor for Alzheimer's disease.<sup>[160]</sup> ApoE also binds low-density lipoprotein (LDL) receptors and plays a central role in plasma lipoprotein metabolism and cholesterol transport.<sup>[161]</sup> In the liver, apoE mediates the binding of lipoprotein remnant to the complex of heparan sulfate PG with the LDL receptor-related protein, facilitating lipoprotein uptake.<sup>[162]</sup>

Both the N- and C-terminal domains contain a putative heparin-binding site.<sup>[163, 164]</sup> The high-affinity heparin-binding site of the N-terminal domain overlaps with the LDL receptor-binding region; the heparin-binding site of the C-terminal domain is only available for interaction in the lipid-free state.<sup>[164]</sup> A third heparin-binding site has been proposed for the segment of protein that connects the N-terminal and C-terminal domains.<sup>[163]</sup> The role of apoE and heparan sulfate PG in the brain has been examined with cultured neurons; the results suggest that the effects of Alzheimer's disease are mediated by the interaction of apoE with the heparan sulfate PG–LDL receptor-related protein complex.<sup>[162]</sup> Based on this model, apoE initially interacts with the heparan sulfate PG on the cell surface and is then transferred to the LDL receptor-related protein receptor for internalization. Thus, interaction with heparan sulfate represents the initial recognition step that localizes the apoE to the cell surface. The interaction of heparin with apoE isoforms has been studied using SPR,<sup>[165]</sup> and a recent study that

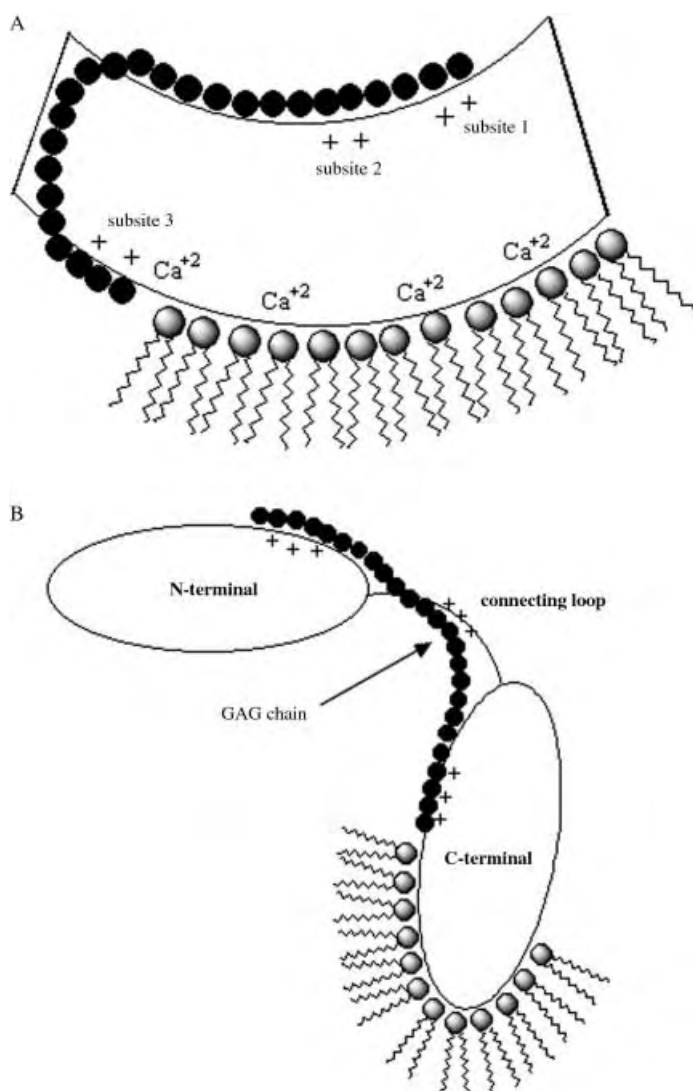


Figure 10. Model for the binding of heparin to lipid-binding proteins by wrapping around. A) Annexin V. B) Apolipoprotein E.

characterized both the energetics and kinetics of the binding of heparin with the N-terminal domain of apoE4 identified an octasaccharide sequence as the minimum binding site within heparin.<sup>[166]</sup> Analysis of these binding data suggests that a heparan sulfate chain wraps around an apoE contacting all three heparin-binding sites (Figure 10B). This model is similar to that proposed for heparin binding to the other lipid-binding protein annexin V (Figure 10A).

## 7. Heparan Sulfate as a Receptor for Pathogens

The initial binding of a virus to a target cell often represents a critical step in pathogenesis.<sup>[167]</sup> Binding may result from a receptor-like interaction between a viral coat protein molecule and the glycosaminoglycan chain of a proteoglycan expressed on the surface of the target cells. Heparan sulfate GAGs are found on the external surface of most mammalian tissues,<sup>[17, 19]</sup> therefore, it is not surprising that viruses make use of these molecules as receptors to bind to and gain entry into target cells.

The interaction of the human immunodeficiency virus type-1 (HIV-1) coat proteins with heparin and heparan sulfate has been the subject of many studies because of the potential of these sulfated polysaccharides in the therapy and prevention of HIV-1 infection.<sup>[168]</sup> The physiological target cells for HIV-1 infection, CD4<sup>+</sup> T-cells, monocytes/macrophages, and some populations of dendritic cells, all express a cellular receptor molecule CD4.<sup>[169]</sup> HIV-1 binds to a loop of 20 amino acids in the first domain of CD4 by interacting with the viral surface glycoprotein, gp120.<sup>[170]</sup> This interaction is believed to induce a conformational change in HIV glycoproteins resulting in the exposure of co-receptor binding sites on gp120.<sup>[171]</sup> The interaction of gp120 and perhaps gp41 with CD4 and the co-receptor molecules ultimately results in the fusion of virus and cell membranes.<sup>[172]</sup>

Heparin exerts its anti-HIV-1 activity by binding to the V3 loop, a major epitope of gp120.<sup>[173]</sup> The V3 loop is not involved in the initial gp120–CD4 binding, but has an essential role to play in subsequent steps leading to membrane fusion.<sup>[174]</sup> Studies with chemically modified heparin molecules show that O-sulfation, particularly 6-O-sulfation, and N-substitution (acetylation or sulfation) are essential for this interaction.<sup>[175]</sup> Another study shows that cell lines lacking the CD4 receptor are still infected by HIV-1 due to an interaction between gp120 and cell surface heparan sulfate. This indicates that CD4 dependence for HIV-1 attachment to target cells is highly cell line specific and in some cases heparan sulfate may act as the cell surface receptor for HIV-1.<sup>[176]</sup> There is also evidence that there might be a step prior to the gp120–CD4 interaction involving cell surface heparan sulfate chains and cyclophilin A (CypA), which would represent the initial step of HIV-1 localization and attachment to the cell surface.<sup>[177]</sup> CypA is an abundant cytosolic protein ubiquitously expressed in eukaryotic cells and is packaged into nascent HIV-1 particles at the time of viral assembly.<sup>[178]</sup> CypA is exposed on the viral membrane and also has a domain of basic residues similar to known heparin-binding motifs.

Heparin and heparan sulfate are also important in another aspect of HIV-1 infection. One of the proteins essential for HIV-1 replication is the Tat protein, which can be released from cells and has autocrine and paracrine (local signaling) activities.<sup>[179]</sup> The Tat protein has the ability to enter cells and is believed to play a role in priming cells for infection. Tat is a heparin-binding protein which also interacts with heparan sulfate proteoglycans on the cell surface and in the extracellular matrix.<sup>[180]</sup> The minimum-sized heparin fragment involved in Tat binding is a hexasaccharide, although the binding affinity increases with increasing oligosaccharide size, with about 18 saccharide residues required to match heparin's affinity.<sup>[181]</sup> Thus, heparin represents a “multi-target” compound capable of affecting different aspects of HIV infection.

The herpes simplex virus (HSV) causes many disease states including mucosal lesions and encephalitis. These diverse clinical manifestations reflect the capacity of the virus to infect both epithelial and neuronal cells. HSV also uses heparan sulfate PG to target<sup>[182]</sup> and infect cells.<sup>[183]</sup> The entry of HSV into mammalian cells is a multi-step process beginning with an attachment step in which viral coat glycoproteins gC and gB interact with heparan sulfate chains on cell surface



proteoglycans.<sup>[184]</sup> HSV types 1 and 2 differ in their interaction with heparan sulfate, which may influence viral tropism.<sup>[185]</sup> These observed differences are the result of different requirements of gC and gB in HSV-1 and HSV-2 for binding heparin/heparan sulfate.<sup>[186]</sup> The second step in the entry of HSV requires the interaction of glycoprotein gD with a specific sequence within the heparan sulfate chains that have been modified by 3-O-sulfation of specific glucosamine residues. This interaction leads to the initiation of HSV-1 entry into the cell.<sup>[70]</sup>

Dengue virus, a mosquito-borne flavivirus, responsible for yellow fever is also believed to target cells by the interaction of an envelope protein with a highly sulfated heparan sulfate (in the liver), which could give an explanation for the tropism of the virus.<sup>[187]</sup> Two putative heparin-binding motifs at the C-terminus of the dengue envelope protein sequence have also been identified (Figure 11). Heparin and a number of

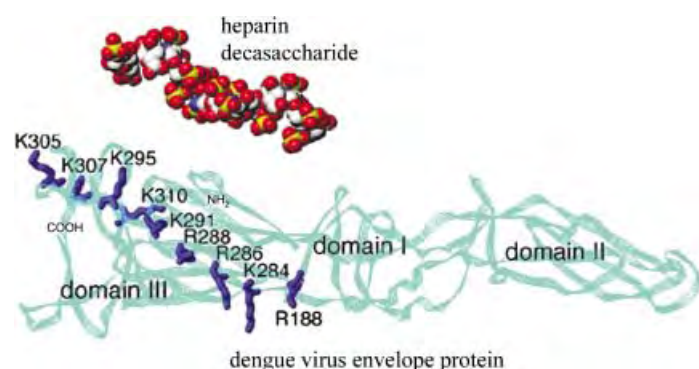


Figure 11. Homology model of the dengue virus envelope protein with a structurally modeled heparin deca-saccharide. The envelope protein is shown in green with the side chains of the basic amino acids (188 and 284–310) shown in blue. These residues form an extended positively charged domain that is externally exposed. The space-filling model of a heparin deca-saccharide having a major disaccharide repeating sequence (Scheme 1) is shown with sulfur (yellow), oxygen (red) and nitrogen atoms (blue).

smaller analogs are being investigated as potential pharmaceutical agents to prevented dengue virus infection.<sup>[187, 188]</sup> Other viruses, such as the respiratory syncytial virus,<sup>[189]</sup> the cytomegalovirus,<sup>[190]</sup> the adeno-associated virus,<sup>[191]</sup> and the foot-and-mouth disease virus,<sup>[192]</sup> all employ heparan sulfate chains of cell surface proteoglycans in their initial step of infection.

Heparin and heparan sulfate are also believed to play an important role in the virulence of other pathogens. The circumsporozoite (CS) protein is a sporozoite cell surface protein of *Plasmodium falciparum*, the parasite causing malaria. The CS protein interacts with the highly sulfated heparan sulfate, present on the surface of liver cells,<sup>[193]</sup> to promote sporozoite attachment and subsequent invasion of the hepatocytes.<sup>[194, 195]</sup> This interaction is inhibited by heparin in a dose-dependent manner.<sup>[196]</sup> The CS protein has been cloned and purified and identified as a heparin-binding protein.<sup>[197]</sup> The uptake of malaria sporozoites by hepatocytes may take place by the same mechanism involved in the apolipoprotein-E-mediated clearance of lipoprotein remnants from the blood by the liver.<sup>[198]</sup> A deca-saccharide, which shares the sequence of an heparin octa-saccharide identified as

the minimum-size oligosaccharide required for binding apoE,<sup>[166]</sup> corresponds to the minimum sequence size for the CS-protein-binding domain.<sup>[195]</sup>

Binding heparin is an efficient strategy utilized by microbial pathogens to recruit a diverse array of mammalian heparin-binding proteins to their surfaces, thus bypassing the need to synthesize individual receptors for each of these proteins.<sup>[199]</sup> Indeed, the human pathogen *Neisseria gonorrhoeae* binds vitronectin, an extracellular matrix protein, without the involvement of a specific vitronectin receptor on its cell surface.<sup>[200]</sup> In this case it is believed that vitronectin binding is indirect and mediated through a heparan sulfate chain that forms stable molecular bridges between the bacterial surface adhesin OpaA and vitronectin, both heparin-binding proteins.<sup>[201]</sup>

## 8. Interaction of Heparin with Adhesion Proteins

The interaction of heparin and heparan sulfate with adhesion proteins has implications in various physiological and pathological processes including inflammation, nerve tissue growth, tumor cell invasion, and plaque formation in the brain.

The selectins (L-, E-, and P-selectin) are a family of transmembrane glycoproteins found on endothelium, platelets, and leukocytes.<sup>[202]</sup> They are responsible for mediating the initial adhesive events directing the homing of lymphocytes into lymphoid organs and the interaction of leukocytes with the endothelium in inflammation and reperfusion injury states.<sup>[203]</sup> Selectin interactions may also be involved in the metastasis of certain epithelial cancers.<sup>[204]</sup> Although the putative ligand on the endothelium responsible for the interaction of leukocytes with selectins is the carbohydrate antigen sialyl Lewis X (SLe<sup>x</sup>), heparan sulfate has also been shown to play a role in this interaction.<sup>[153, 205]</sup> Heparan sulfate interacts with L- and P-selectin, but not E-selectin.<sup>[153, 206]</sup> The interaction of heparin with L-selectin is calcium-dependent and requires micromolar levels of free calcium. L-selectin binds oligosaccharides that contain highly modified, heavily sulfated, iduronate rich regions and endothelial tissue-derived heparan sulfate chains that are enriched in free amino groups.<sup>[207]</sup> The P-selectin-binding heparan sulfates include chains with less highly modified domains.<sup>[206]</sup> Heparin tetra-saccharides specifically block the interactions of L- and P-selectins with SLe<sup>x</sup>-containing ligands demonstrating anti-inflammatory activity in vivo, and also prevent colon cancer cell adhesion to L- and P-selectin.<sup>[205]</sup>

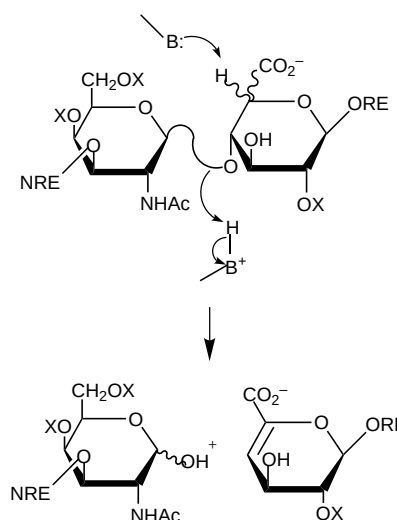
The heparin-binding growth-associated molecule (HB-GAM), or pleiotrophin, is another protein associated with the extracellular matrix. HB-GAM is believed to play a role in enhancing neurite outgrowth by providing extracellular tracts to guide neurites in the developing brain.<sup>[208]</sup> A heparan sulfate PG, syndecan-3, binds with high affinity to HB-GAM and may be a receptor for HB-GAM. This binding mediates neurite outgrowth promoting signals from growing neurites.<sup>[209]</sup> Soluble heparin and heparan sulfate GAGs are inhibitory towards neurite outgrowth, and the presence of 2-O-sulfo groups is required for inhibitory effects. A heparin

decasaccharide was required for the inhibition of HB-GAM-induced neurite outgrowth, and maximum activity was observed for an octadecasaccharide.<sup>[210]</sup> ITC and SPR were used to study the thermodynamics and kinetics of the heparin–HB-GAM interaction.<sup>[86]</sup> ITC studies demonstrated a stoichiometry of interaction corresponding to a heparin binding site for HB-GAM of 12–16 saccharide residues. Affinity chromatography on HB-GAM-Sepharose showed that oligosaccharides with more than 18 saccharide residues gave the strongest interactions. CD and NMR spectroscopy revealed that HB-GAM undergoes a conformational change upon binding to heparin and that the binding occurs primarily through the  $\beta$ -sheet domains of HB-GAM.<sup>[211]</sup> A search of sequence databases shows that the  $\beta$ -sheet domains of HB-GAM are homologous to the thrombospondin type I repeat (TSR). The TSR sequence motif occurs in a wide variety of proteins (including malaria CS protein) that mediate cell-to-extracellular matrix and cell-to-cell interactions, in which the TSR domain mediates specific cell surface binding.

Heparin and heparan sulfate are also believed to be involved in the formation of amyloid deposits in Alzheimer's disease and are found in associated senile plaques and neurofibrillary tangles.<sup>[212]</sup> The amyloid P (AP) component is a glycoprotein found in the circulation, in basement membranes, and in connective tissue and is also a universal constituent of the abnormal tissue deposits in amyloidosis, including Alzheimer's disease.<sup>[213]</sup> AP has been shown to bind to heparin, heparan sulfate, and dermatan sulfate in a calcium-dependent manner.<sup>[152]</sup> AP also exhibits a calcium-independent binding of lower affinity to heparan sulfate and dermatan sulfate, and this binding is enhanced under conditions of slightly lowered pH, possibly due to the protonation of histidine residues in AP.<sup>[214]</sup> Two heparin-binding fragments have been identified in the proteolytic digests of AP.<sup>[215]</sup> The fragment sequences do not correspond to any previously reported heparin-binding sequences and unlike AP these peptides did not require calcium for binding activity. The binding of the peptide that exhibited the highest affinity for heparin was characterized by affinity capillary electrophoresis.<sup>[216]</sup> This binding was found to be highly specific for heparin and heparin oligosaccharides down to tetramers and appeared stronger at a slightly alkaline pH. No binding could be demonstrated with heparan sulfate, chondroitin sulfate, and desulfated heparin. While the precise role of heparin and heparan sulfate in Alzheimer's disease pathology is still unknown, there is a possibility that heparin or heparin oligosaccharides may be useful agents in slowing or reversing the formation of Alzheimer's<sup>[217]</sup> and prion-based plaques in the brain.<sup>[218]</sup>

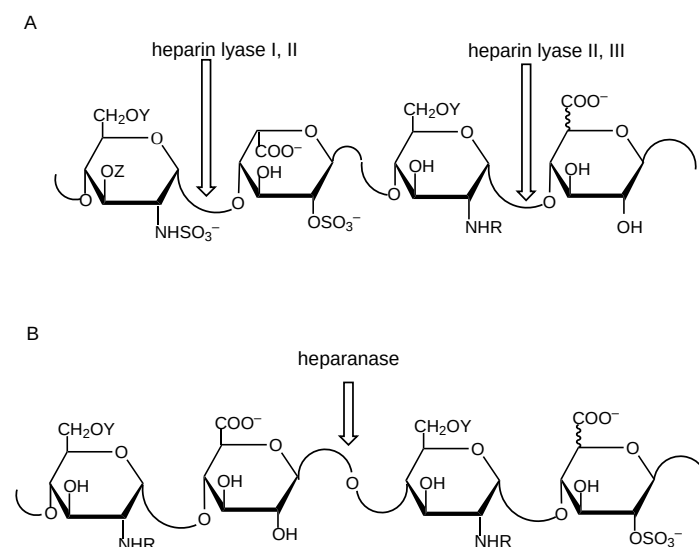
## 9. Heparin-Degrading Enzymes

Two types of enzymes act on heparin and heparan sulfate, the prokaryotic polysaccharide lyases (acting through an eliminative mechanism)<sup>[35]</sup> and the eukaryotic glucuronyl hydrolases (acting through a hydrolytic mechanism). Heparin lyases eliminatively depolymerize heparin affording unsaturated oligosaccharide products (Scheme 5). Three major



Scheme 5. Proposed mechanism for the eliminative depolymerization of glycosaminoglycans. B represents a basic moiety, X = H or  $\text{SO}_3^-$ .

polysaccharide lyases (heparin lyases I, II, and III), isolated from *Flavobacterium heparinum*, are capable of cleaving linkages present in heparin and heparan sulfate.<sup>[12]</sup> The substrate specificity of each of these enzymes has been well studied using heparin-derived oligosaccharides and chemically modified heparins (Scheme 6 A).<sup>[13]</sup>



Scheme 6. Substrate specificity of A) heparin lyases I, II, and III, B) mammalian heparanase (Y, Z = H or  $\text{SO}_3^-$ , R = Ac or  $\text{SO}_3^-$ ).

Alignment of the primary sequences of these enzymes revealed little sequence homology at both the DNA and the amino acid levels.<sup>[219]</sup> There are three basic clusters in heparin lyase II that resemble heparin-binding consensus sequences. These share homology with a basic cluster in the heparin-binding site of heparin lyase I and two basic clusters in heparin lyase III. There are two putative “EF-hand” calcium-coordinating motifs in heparin lyases I and III and none in heparin lyase II,<sup>[219]</sup> consistent with the observation that calcium enhances the enzymatic activity of heparin

lyases I and III but inhibits enzymatic activity of heparin lyase II.<sup>[12]</sup>

The genes encoding the three heparin lyases in *Flavobacterium heparinum* have been cloned and expressed in *Escherichia coli*.<sup>[220, 221]</sup> Studies on the enzymology of heparin lyase I have identified a cysteine and a histidine residue as part of the catalytic domain<sup>[222]</sup> and shown that three lysine residues are involved in heparin binding close to the catalytic site.<sup>[223]</sup> Heparin lyase II has the broadest substrate specificity of the three heparin lyases. It is known to have two distinct active sites, one believed to act on heparin and the other on heparan sulfate.<sup>[224]</sup> One cysteine and three histidine residues have been identified as crucial for heparin lyase II activity.<sup>[225]</sup> Heparin lyase III, exhibiting a strong specificity for heparan sulfate, is unique in that it contains no cysteine residues<sup>[221, 226]</sup> but instead two histidine residues crucial for its activity on heparan sulfate.<sup>[227]</sup>

These enzymes are essential in the preparation of defined oligosaccharides from heparin and heparan sulfate required for the structural characterization of heparin and heparan sulfate.<sup>[14]</sup> They are also important clinically and have been used in the monitoring of heparin levels in the blood,<sup>[228]</sup> the neutralization of heparin in the blood and the production of LMW heparins for use in humans.<sup>[8, 229]</sup> Recent studies show that heparin lyase I and II are capable of cleaving the AT-III-binding site within heparin leaving only a partial site which lacks some of the functional attributes of heparin with an intact AT-III-binding site.<sup>[230]</sup> Heparin lyase I and III are also potent inhibitors of neovascularization, which is associated with the regulation of tissue development, wound healing, and tumor metastasis.<sup>[231]</sup> A novel type of heparin lyase recently purified from *Bacteroides stercoris* HJ-15, isolated from human intestine,<sup>[232]</sup> may be important in understanding how to improve the oral bioavailability of pharmaceutical heparin.<sup>[233]</sup>

Human heparanase, which is an *endo*- $\beta$ -D-glucuronidase capable of cleaving heparan sulfate, has been purified, cloned, and characterized.<sup>[234]</sup> Heparanase is a hydrolase, distinct from the flavobacterium heparin lyases, and has been implicated in inflammation as well as in tumor angiogenesis and metastasis, making it an important target for the development of inhibitors.<sup>[235]</sup> Heparanase is known to cleave heparan sulfate into characteristic large-molecular-weight fragments.<sup>[236]</sup> Studies on the substrate specificity of this enzyme suggest the importance of 2-O-sulfo groups on uronic acids (Scheme 6B).<sup>[237]</sup> The optimal pH for the heparanase activity is 4.2, implying that it might be localized in the lysosomes.<sup>[237]</sup>

## 10. New Clinical Applications of Heparin

The interaction of heparin with various proteins that play important roles in the regulation of normal physiological processes as well as disease states has lead to an interest in using heparin in roles outside its normal application as an anticoagulant/antithrombotic agent. Randomized trials to study the effectiveness of LMW heparin as compared to unfractionated heparin in treating venous thromboembolism in cancer patients led to a surprising observation: treatment with heparin may affect survival of patients with malignan-

cy.<sup>[238]</sup> Cancer patients who had been treated with LMW heparin for their thrombosis showed a slightly improved three-month survival rate as compared to cancer patients receiving unfractionated heparin. Heparin can potentially exert its activity at various stages in cancer progression and malignancy-related processes. It can affect cell proliferation, interfere with the adherence of cancer cells to the vascular endothelium, regulate the immune system and have both inhibitory and stimulatory effects on angiogenesis.<sup>[239]</sup> There is recent evidence that heparin treatment reduces tumor metastasis in mice by inhibiting P-selectin-mediated interactions of platelets with mucin ligands on carcinoma cell surfaces.<sup>[240]</sup>

Numerous proteins of physiologic and pathophysiologic importance interact with heparin and heparan sulfate. This offers a large number of potential therapeutic applications for heparin. The major limitation in utilizing heparin in new ways is that its high potency as an anticoagulant becomes a side effect that can lead to hemorrhagic complications. The introduction of LMW heparins and the preparation of heparin oligosaccharides and synthetic analogs devoid of anticoagulant activity may open up a wide variety of new therapeutic applications in the treatment of cancer, viral and bacterial infections, Alzheimer's disease, and transplant rejection.

## 11. Summary and Outlook

Over the last few decades heparin and heparan sulfate have been shown to interact with a number of biologically important proteins, thereby playing an essential role in the regulation of various physiological processes (Figure 12). Our

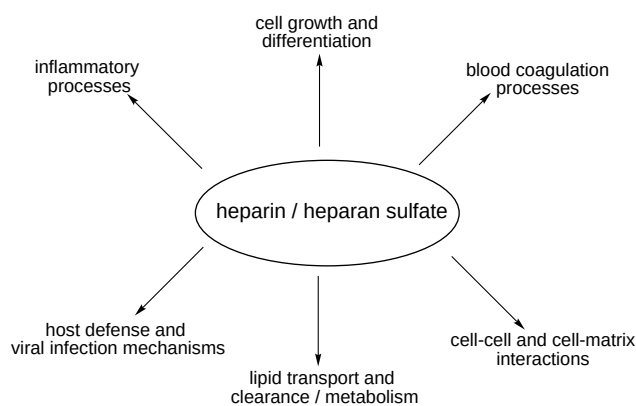


Figure 12. Involvement of heparin and heparan sulfate in important physiological processes.

understanding of these interactions at the molecular level is important for the design of highly specific therapeutic agents. In addition, an understanding of the specificity of heparin and heparan sulfate will be necessary to understand normal physiologic and pathophysiologic processes. These processes are particularly important wherever cell–cell interaction plays an important role, such as in developmental biology, cancer, wound healing, infectious diseases, inflammatory processes, and neurite outgrowth.

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The second world summit on sustainable development will be held this year in Johannesburg. The central theme is the conservation and control of resources. A substantial contribution must be made to this by science, whereby the combination of ecological, economical, and social science needs are consolidated to meet the challenges of the future.



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## 10 Years after Rio—Concepts on the Contribution of Chemistry to a Sustainable Development

Marco Eissen, Jürgen O. Metzger,\* Eberhard Schmidt, and Uwe Schneidewind

The principles of the United Nations Conference on Environment and Development (UNCED), held in June 1992 in Rio de Janeiro, and Agenda 21, the comprehensive plan of action for the 21st century, adopted 10 years ago by more than 170 governments, address the pressing problems of today and also aim at preparing the world for the challenges of this century. The conservation and management of resources for development are the main focus of interest, to which the sciences will have to make a considerable contribution. Natural, economic, and social sciences will have to be integrated in order to achieve this aim. In their future programs, the associations of the chemical industries in Europe, Japan, and the USA have explicitly accepted their obligation to foster a sustainable

development. In this review we investigate innovations in chemistry exemplarily for such a development with regard to their ecological, economical, and social dimensions from an integrated and interdisciplinary perspective. Since base chemicals are produced in large quantities and important product lines are synthesized from them, their resource-saving production is especially important for a sustainable development. This concept has been shown, amongst others, by the example of the syntheses of propylene oxide and adipic acid. In the long run, renewable resources that are catalytically processed could replace fossil raw materials. Separation methods existing today must be improved considerably to lower material and energy consumption. Chemistry might become the

pioneer of an innovative energy technique. The design of chemical products should make possible a sustainable processing and recycling and should prevent their bio-accumulation. Methods and criteria to assess their contribution to a sustainable development are necessary. The time taken to introduce the new more sustainable processes and products has to be diminished by linking their development with operational innovation management and with efficient environmental-political control procedures.

**Keywords:** environmentally friendly synthesis • innovations • oxidations • renewable raw materials • sustainable development

### 1. Introduction

Principle 1 of the “Rio declaration on Environment and Development”, (Rio declaration) of the United Nations Conference on Environment and Development (UNCED) in June 1992 proclaims: “Human beings are at the center of concerns for sustainable development. They are entitled to a

healthy and productive life in harmony with nature.”<sup>[1]</sup> The world population will rise from the present 6 billion people—1.2 billion of these in the industrialized countries—to 8–11 billion in the year 2050; the National Research Council of the USA considers a population number of 9 billion to be most likely.<sup>[2]</sup> This growth will unfold nearly exclusively in the developing countries of today, namely in Africa, Asia, and Latin America, thus causing a change in the ratio of the population in the developing countries to that in the industrial countries from 4:1 today to 7:1. The standard of life in the developing countries has to grow and has to adapt more and more to the one in the industrial countries, which must not drop if Principle 3 of the Rio Declaration of a sustainable development has to be met: “The right to development must be fulfilled so as to equitably meet developmental and environmental needs of present and future generations”, or in the frequently quoted words of the Brundtland report: “Sustainable development is development that meets the needs of the present without compromising the ability of

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future generations to meet their own needs”.[3] In addition to the demand for food, the demand for other goods will grow substantially. The demand for goods will more than double, and with an increasing adaption of the standard of living it will soon grow by a factor of four and more. Resources will have to be used much more efficiently than today, that is, multiple goods will have to be produced with the same or even a lower quantity of resources. Therefore, measures have to be intensified to lower significantly the use of resources per unit of usage. A lowering by a factor of four will not be sufficient since the existing fossil resources will be increasingly difficult to access.[4, 5] Therefore, it has to be assumed that the oil production will already have passed its maximum in this decade, at the latest by 2015–2020, and will then slowly decrease.[6] The increase in the efficiency of resource usage refers to Principle 8 of the Rio Declaration: “To achieve sustainable development and a higher quality of life for all people, States should reduce and eliminate unsustainable patterns of production and consumption and promote appropriate demographic policies”, whereby, as a further essential issue, the protection of the environment addressed in Principle 4 has to be considered: “In order to achieve sustainable development, environmental protection shall

constitute an integral part of the development process and cannot be considered in isolation from it.”

The Principles of the Rio conference were made concrete in Agenda 21, the comprehensive plan of action for the 21st century which was adopted by more than 170 governments.[7] Agenda 21 “addresses the pressing problems of today and also aims at preparing the world for the challenges of the next century” (Chapter 1.3). The “Conservation and management of resources for development” are the main focus of interest (Agenda 21, Part II). The sciences have to make a considerable contribution if this aim is to be achieved. “There is a need for the sciences constantly to reassess and promote less intensive trends in resource utilization ... Thus, the sciences are increasingly being understood as an essential component in the search for feasible pathways towards sustainable development” (Agenda 21, Chapter 35.2) by “integrating physical, economic and social sciences in order better to understand the impacts of economic and social behavior on the environment and of environmental degradation on local and global economies” (Agenda 21, Chapter 35.11c). This, however, means nothing else than requesting scientists to develop basic and applied research topics from the immense catalogue of unsolved problems outlined in Agenda 21.



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Though not sufficiently realized to date, this also applies to chemistry.

During the last ten years, essential aspects of the Rio Declaration<sup>[1]</sup> and Agenda 21<sup>[7]</sup> have been tackled. The Enquete commission "Protection of Man and the Environment" of the German Bundestag investigated both the prospects for a sustainable handling of the flow of materials and substances<sup>[8]</sup> and the implementation of the model sustainability into the social reality of the 21st century. It came to the conclusion that the overall objective of the sustainability effort is to secure and improve ecological, economic, and social productivity.<sup>[9]</sup> The safety of chemicals, which in Agenda 21 is addressed in the separate chapter 19, has been improved significantly by international agreements,<sup>[10]</sup> to which the worldwide voluntary initiative "Responsible Care" of the chemical industry contributes considerably.<sup>[11]</sup>

In their future programs, the chemical industries of Europe, Japan, and the USA have explicitly accepted the contribution of chemistry to sustainable development.<sup>[12, 13]</sup> However, the participation of the chemical industry in the USA in the future program Vision 2020 seems to occur at a lower level than expected, and the Synthetic Organic Chemical Manufacturers Association (SOCMA) has even withdrawn its active support since the interests of smaller sized firms are not met.<sup>[13b]</sup> In general, it must be said, that the chemical companies are attempting to understand the implications of sustainable development for them.<sup>[14]</sup>

The principles of production- and product-integrated environmental protection are increasingly accepted and implemented by numerous enterprises.<sup>[15, 16]</sup> Basic concepts for an environment-oriented design of chemical products and processes have been developed.<sup>[17]</sup> "Green Chemistry" was proposed as an orientation for basic research in chemistry.<sup>[18]</sup>

In this review we want to investigate exemplarily innovations in chemistry for sustainable development from an integrated and interdisciplinary point of view at five levels—the process, product, evaluation, organizational, and socio-political levels—largely based on the reports presented at a corresponding conference in February 2000.<sup>[19a]</sup>

Since base chemicals—namely chemicals that are each produced worldwide in more than a million tons per annum (t/a)—are produced in large quantities and important product lines are synthesized from them, their resource-saving production is hence especially important for sustainable development.<sup>[19b]</sup> This calls for the development of new processes for certain base chemicals or even completely new base chemicals. The base chemicals affect directly the chemical products that are produced from them in one or several steps, they are then processed in fields of industry that frequently do not belong to the chemical industry. These chemical products need to be designed in such a way that they can be processed in a sustainable way. Methods and criteria for the evaluation of their sustainability are necessary at the earliest possible stage of the development process. The time taken to introduce the new more-sustainable processes and products has to be diminished by linking their development with operational innovation management as well as with efficient environmental-political control procedures.

In the discussion on the contribution of chemistry to sustainable development it is often regretted that the term "sustainability" is used in an inflationary way and that there is no longer an exact definition. Therefore, a precise definition of the term is all the more urgent. We comprehend sustainability as the implementation of the Rio Declaration and Agenda 21 including its on-going advancement, such as is planned for the year 2002 in Johannesburg. How chemistry can and must contribute to this is outlined in this review.

## 2. On the Way to Environment- and Resource-Saving Syntheses and Processes

The energy and environmental profile of the chemical industry in the USA has been investigated and described recently in detail.<sup>[20]</sup> In 1997, the chemical industry used 6650 PJ (Peta =  $10^{15}$ ) of energy, which represents about 7 % of all domestic energy used and 25 % of the energy consumed in all manufacturing processes. Approximately 51 % of the total was used as feedstock for chemical products (non-energetic consumption) and 49 % as process energy for carrying out the processes (energetic consumption). The main energy consumption at 2640 PJ is invested in the production of the organic base chemicals (Figure 1).

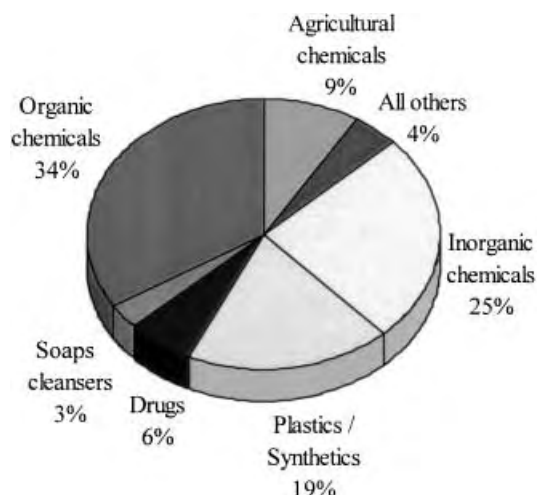


Figure 1. Distribution of gross energy requirements (GER) of the chemical industry in the USA by product groups.<sup>[20]</sup>

An investigation of the most important value-adding chains based on ethylene, propylene, BTX (benzene, toluene, xylene), and butadiene and additionally comprising inorganic chemicals and fertilizers has shown a consumption of 1690 PJ process energy for these and an estimated potential energy saving of approximately 30 %. Analysis of the production output of the chemical industry from 1974–1997 shows, however, that the energy consumption per unit of emission declined by more than 39 % between 1974 to 1988 but since then it has stagnated, while the total energy consumption from 1974 to 1997 has risen, as a result of the continuous growth of the chemical production by 80 %. This makes us conclude that the relatively low-cost, high-return energy investments have

already been undertaken. Further gain will require more dramatic changes in process design and in innovative solutions yet to be provided by research and development. If the intention to reduce by the year 2020 the energy consumption of the chemical industry per product unit by 30 % of that at the end of the 20th century<sup>[13]</sup> can be realized, this will be an important contribution to sustainable development. However, this will not be sufficient, since the total energy consumption of the chemical industry will remain constant or even increase as a result of the further increase in production. Furthermore, chemistry makes major contributions to a more efficient provision of energy<sup>[21a]</sup> and is also the pioneer of innovative energy techniques.<sup>[21b]</sup>

An estimation of the material, energy, and CO<sub>2</sub> flows for the chemical industry in Germany in 1995 showed there was a primary energy (see glossary) demand of approximately 1700 PJ, whereof 830 PJ was stored in synthetic organic products (non-energetic use).<sup>[22, 23]</sup> This value comprises the use of feedstock, the total chain of processing, and waste treatment, and corresponds to 44 % of the primary energy use of all manufacturing processes or 12 % of the total energy consumption of Germany. A potential saving of process energy of 250 PJ, which corresponds to a total primary energy saving of 14 % by the year 2005, was identified. The CO<sub>2</sub> emissions amounted to approximately  $57 \times 10^6$  t, which is about 20 % of all manufacturing and 6 % of the total emissions. The potential reduction by the year 2005 was estimated at  $16 \times 10^6$  t.<sup>[23a]</sup> With the “Agreement on Climate Protection between the Government of the Federal Republic of Germany and German Business” of November 11, 2000, the specific CO<sub>2</sub> emissions and energy consumption will be lowered by 20 % of the 1990 values by the year 2005.<sup>[24]</sup>

The ratio of the primary energy input in the USA and in Germany corresponds quite well with the ratio of the chemistry turnover in both countries of  $733 \times 10^9$  DM and  $187 \times 10^9$  DM, respectively, in the year 1998. It can be assumed that similar data can be obtained for all developed industrial countries. These estimations show that the present processes of the chemical industry can become more efficient, but they also show that it is impossible to produce twice or even four times the present quantity of goods. Basic innovations for the production of the necessary goods combined with a significantly lower need of resources—approximately a tenth—are necessary.<sup>[5]</sup>

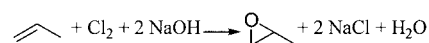
## 2.1. Catalytic Direct Oxidations

Oxidations belong to the most important reactions in organic chemistry. However, they cause the strongest stress on the environment. It is remarkable how poorly these direct oxidations with oxygen are understood and controlled.<sup>[25, 26]</sup> Here, as shown by the example of propylene oxide, a breakthrough would be a substantial contribution of chemistry to sustainable development.

Propylene oxide is one of the top 50 chemicals in terms of production: in 1997,  $1.9 \times 10^6$  t were produced in the USA, about  $1 \times 10^6$  t were produced in Germany, and approximate-

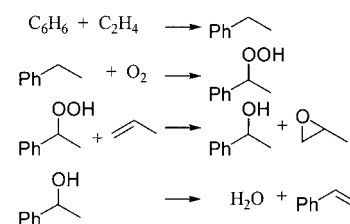
ly  $4 \times 10^6$  t were produced worldwide. In the USA—and this distribution is typical for the world market—65–70 % is reacted via polyether polyols to form polyurethane foams and 22 % to form propyleneglycol.<sup>[27]</sup> Propylene oxide was investigated and described in detail by the Enquete Commission of the German Bundestag as an example of a chlorine-free end product produced using chlorine.<sup>[8a]</sup> Industrial processes used are:<sup>[27]</sup>

- chlorohydrin processes (Scheme 1)
- oxirane processes with isobutane or ethylbenzene (Scheme 2).



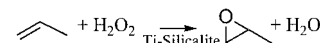
Scheme 1. Production of propylene oxide by the chlorohydrin process. The masses of compounds per ton of propylene oxide are: propene: 0.763 t, chlorine: 1.285 t, sodium hydroxide: 1.4 t, sodium chloride: 2.01 t; by-product: 1,2-dichloropropane: 0.102 t; necessary process water: 38 t.<sup>[27]</sup>

Both are indirect processes and the first one in particular is extremely polluting. The oxirane process is a rather more indirect process for the synthesis of *tert*-butyl alcohol and styrene; economically, it can only be done if these coupled products can be sold (Scheme 2). At present, this is the case with styrene, but this is no longer the case with *tert*-butyl alcohol since *tert*-butyl methyl ether is no longer used as an additive to gasoline. However, since additional process steps are required, a compulsory formation of coupled products is always less advantageous than a direct process.



Scheme 2. Production of propylene oxide by the oxirane process with styrene as a coupled product. The reaction sequence starts with the production of ethylbenzene. The masses of the substrates and of the coupled product per ton of propylene oxide are: benzene: 2.11 t, ethene: 0.7 t, propene: 0.88 t, styrene: 2.54 t.<sup>[27]</sup>

During the last few years, the epoxidation of propylene with titanium silicalite/hydrogen peroxide (yield > 90 %) has been developed. (Scheme 3) This process requires hydrogen peroxide, which is both a more reactive but also a more expensive surrogate for oxygen. Hydrogen peroxide can be formed by the alkyl anthrahydroquinone/alkyl anthraquinone process in situ, whereby only water is generally formed as “waste” and yields of propylene oxide of up to 57 % have so far been obtained.<sup>[28]</sup>



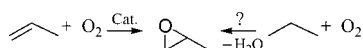
Scheme 3. Oxidation of propylene with H<sub>2</sub>O<sub>2</sub> to propylene oxide using Ti-silicalite as a catalyst.<sup>[28]</sup>

In its investigation in 1994, the Enquete Commission of the German Bundestag has pointed out that there would be a new investment cycle for the existing propylene oxide plants at the beginning of the new millennium.<sup>[8b]</sup> This is in fact the case:



most of the chlorohydrin plants will be closed down. Bayer and Lyondell have announced the construction of a propylene oxide plant in Europe based on the oxirane procedure with an annual output of 285 000 t of propylene oxide and 640 000 t of styrene.<sup>[29]</sup> New plants using this procedure are also being built in the USA. A Sumitomo Chemical propylene oxide plant that is set to open in Japan in 2003 is based on the use of cumene in the oxirane process. The dimethylbenzyl alcohol coproduct will be dehydrated and hydrogenated back to cumene.<sup>[29]</sup> Degussa, however, will start a large-scale catalytic oxidation of propylene with hydrogen peroxide.<sup>[30]</sup>

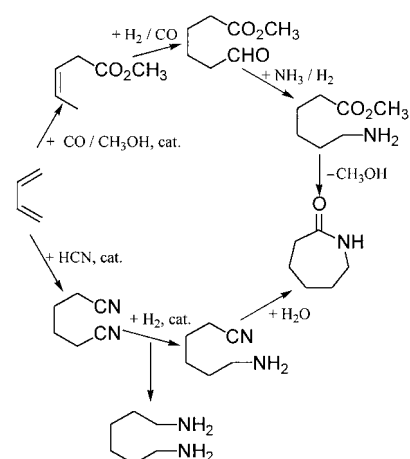
It has finally become very clear that the direct oxidation of propylene or, even better, of propane with oxygen from the air has to be developed for the next investment cycle (Scheme 4). An interesting attempt carried out with oxygen



Scheme 4. Direct oxidation of propene and propane with oxygen to propylene oxide.

is the oxidation of propylene to propylene oxide with gold catalysts on a titanium oxide support.<sup>[31]</sup> It is a disadvantage of this procedure that hydrogen for the reaction of the second oxygen atom has to be added and that more than stoichiometric amounts of water are developed, and hence, the catalyst also catalyzes the oxyhydrogen gas reaction. Other catalysts, for example, bimetallic M/Ti-silicalites (M = Pd, Pd-Pt, Au) have also been described.<sup>[32, 33]</sup> So far, no attempt has been made to achieve the direct oxidation of propane to propylene oxide with oxygen from the air, a process which would be extremely interesting from energetic and feedstock points of view. As long as propylene oxide is used, it is absolutely necessary to thoroughly investigate the direct oxidation of alkenes or alkanes in order to introduce a new, more-sustainable process over the years to come. Additionally, alternatives to propylene oxide have to be investigated.

Caprolactam and adipic acid are further important base chemicals produced by oxidation that have a high demand in resources and whose synthetic processes should be improved to be environmentally more benign.  $\epsilon$ -Caprolactam (world capacity approximately  $4.4 \times 10^6$  t/a) is produced on the  $C_6$  route from cyclohexanone oxime by Beckmann rearrangement, whereby two or three moles of ammonium sulfate are formed. In the Enichem procedure of oxidation of ammonia with  $H_2O_2$  on titanium silicalite, hydroxylamine and hence cyclohexanone oxime are obtained without the necessary formation of ammonium sulfate.<sup>[34]</sup> The Sumitomo process makes possible the heterogeneous catalyzed Beckmann rearrangement in the gas phase without formation of ammonium sulfate.<sup>[36]</sup> The  $C_4$  route of DuPont leads from butadiene via adipic dinitrile, partial hydrogenation, and gas-phase rearrangement to  $\epsilon$ -caprolactam.<sup>[36]</sup> This route also enables the production of hexamethylenediamine for nylon 6.6 through a complete hydrogenation of adipic dinitrile. Alternatively, butadiene can be selectively carbonylated and hydroformylated in two catalytic steps. In this way, caprolactam is obtained in a four-step process (Scheme 5). However, a



Scheme 5.  $C_4$  route of butadiene to  $\epsilon$ -caprolactam and hexamethylenediamine.<sup>[36]</sup>

comparison of the different processes which are currently under realization shows that only rather small innovative steps are being made. The major breakthrough is yet to be achieved in this area.

Adipic acid, which is produced industrially by oxidation of a mixture of cyclohexanone and cyclohexanol (obtained by catalytic air oxidation of cyclohexane) with  $HNO_3$  under formation of the coupled product  $N_2O$  and different nitrogen oxides, is also a basic chemical, the production of which should be improved to be more sustainable<sup>[35]</sup> (see Figure 5). The process was improved by use of the coupled product for energy production<sup>[16b,c]</sup> and for the oxidation of benzene to phenol.<sup>[36]</sup> However, it should be possible to obtain adipic acid by direct oxidation of hexane with air. Recently, there has been a breakthrough in this field. It was possible to oxidize hexane with air directly to adipic acid by means of an aluminum phosphate molecular sieve supported by cobalt(III) on the inner walls of the cage.<sup>[37]</sup> Immense progress has also been made in the catalytic oxidations of cyclohexane<sup>[38]</sup> and cyclohexene<sup>[39]</sup> to adipic acid. The advantages of the catalytic process compared to the classical process have recently been discussed by Thomas et al.<sup>[40]</sup>

All these examples substantiate that the development of more effective catalysts and more selective catalytic processes that lead to the desired product as directly as possible plays a key role.<sup>[41]</sup> An excellent overview on the relevance of catalysis for carbon management has recently been published.<sup>[26]</sup> High-throughput syntheses of catalysts and for the fast testing of very small amounts of catalysts in the various processes are necessary for the effective development of catalysts. Electro-spray-ionization mass spectrometry is a very promising technique for monitoring homogeneous catalytic processes.<sup>[42]</sup>

## 2.2. Use of the Synthesis Output and Synthesis Methods of Nature

The encouragement of environmentally sound and the sustainable use of renewable natural resources (Agenda 21, Chapter 4.18, 16.1a) and biotechnology (Agenda 21, Chapter 16) is one aim of Agenda 21.

### 2.2.1. Renewable Raw Materials

At present, the share of renewable raw materials in the feedstock consumption of the chemical industry in Germany and in the USA runs to approximately 10 %; in Germany, this amounts to 1.8 million t. It is assumed that this percentage will increase notably.<sup>[43]</sup> In the long run, renewables are the only workable solution, and their catalytic processing will make it possible to replace oil and coal as basic feedstocks.<sup>[41]</sup> The National Research council of the USA has recently presented its investigations on the estimated development of renewable feedstocks up until 2090. In 2020 25 % of the production of organic chemical products is expected to come from renewable feedstocks (Figure 2).<sup>[44]</sup>

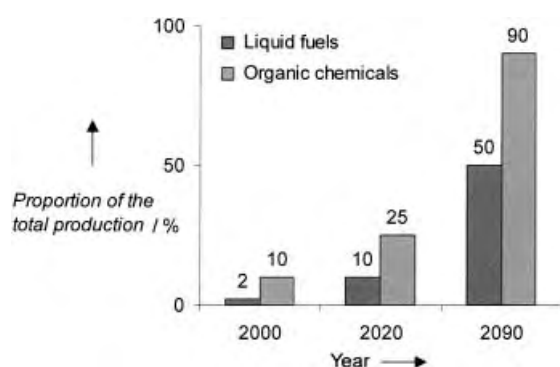


Figure 2. Targets of the National Research Council of the USA for the biobased production of organic chemicals and of liquid fuels by the year 2090. The proportion of the total production of each is given in percent.<sup>[44]</sup>

Approximately 51 % of the renewable raw materials used at present in Germany are fats and oils. Carbohydrates constitute the second largest portion at 43 %, while a further 6 % is made up of other renewables such as proteins and protein surfactants.<sup>[43, 23e]</sup> When renewables are used as base chemicals for organic synthesis, nature's synthetic input has to be used to obtain from the natural chiral pool in one or only a very few chemical reaction steps those complex molecules which petrochemically are only accessible in multistep reaction sequences (see Section 4).

In contrast to the fossil raw materials, renewables are more or less highly oxidized. Therefore, it is clear that for base chemicals that are obtained petrochemically through non-sustainable oxidation reactions, alternatives need to be developed from re-growing raw materials.<sup>[45, 46]</sup> Many highly oxidized industrial chemical products based on starch are available and are further developed.<sup>[47]</sup> Alkyl polyglucosides are a good example; they are produced as skin-compatible, environmentally benign tensides on a scale of 70 000 t/a.<sup>[48]</sup> Only recently, a review of new syntheses with oils and fats as renewable raw materials for the chemical industry was presented.<sup>[49]</sup> The transition metal catalyzed metathesis of unsaturated fatty acids produces  $\omega$ -alkenoic acids; for example, 9-decenoic acid is obtained from oleic acid and 12-tridecenoic acid is obtained from erucic acid.<sup>[50, 51]</sup> The catalytic oxidative cleavage of unsaturated fatty acids yields dicarboxylic acids such as azelaic acid.<sup>[52, 53]</sup> All these chemical compounds are potential base chemicals. The epoxidation of

unsaturated fatty compounds leads to epoxides of fats which can be used as coating binders, and once ring-opened by water as polyol components for polyurethanes.<sup>[54]</sup> The oxidative cleavage of petroselinic acid (6-octadecenoic acid), the main fatty acid of the seed oil of coriander, gives access to adipic acid and a coupled product lauric acid. Adipic acid is also accessible from glucose in a biocatalytic process.<sup>[55]</sup>

Most products obtained with these syntheses from renewable raw materials are at present not competitive with the products of petrochemistry, a circumstance that will change rapidly when oil resources diminish and the oil price rises. Therefore, it is high time to expand basic research to achieve substitution processes and products.

### 2.2.2. Chemical Biotechnology

"Chemical biotechnology" is the quickly spreading application of biotechnology in chemical production.<sup>[56]</sup> The estimated annual market share of biotechnological procedures in the chemical industry of Europe, Japan, and the USA amounts to 1–2 %, in which biotechnological procedures are mainly employed for the production of fine chemicals and pharmaceuticals.<sup>[57]</sup> The use of biocatalysis for the industrial synthesis of fine chemicals is increasing rapidly.<sup>[58]</sup> Here, the driving force is certainly not sustainability but the fact that a nonbiocatalytic process is not possible or would be extremely disadvantageous economically. The production of base chemicals using biotechnology is only gaining recognition at a slow pace. Besides the classical procedures for ethanol (world production in 1991: 12.6 million tons<sup>[57]</sup>), sorbitol, and citric acid, only the lipase-catalyzed hydrolysis of acrylonitrile to acrylamide by the Nitto Chemical Company with 30 000 t/a has been achieved. The production of bio-ethanol will first increase considerably in the USA from the present  $6 \times 10^6$  t to  $10.5 \times 10^6$  t in 2003 by the substitution of *tert*-butyl methyl ether (MTBA) as a gasoline additive.<sup>[59]</sup> It is remarkable that the addition of ethanol to gasoline as an antiknock compound was already known in 1917 and that in 1923, however, General Motors, DuPont, and Standard Oil pushed for the use of tetraethyl lead—despite its long-known toxicity—for patent reasons.<sup>[60]</sup> It must be assumed that the biotechnological production of base chemicals would be much more developed today if the sustainable decision had been made for ethanol in 1923. Moreover, the fine distribution of millions of tons of lead all over the world— $7 \times 10^6$  t in the USA alone—would have been prevented. The amount is increasing still further since tetraethyl lead is still produced and sold to Third World countries.<sup>[60]</sup> This is an impressive example that clearly shows how important it is to steer towards the aims of sustainable development, especially in the highly developed countries, as defined in the Rio Declaration and Agenda 21.

### 2.3. Separation Processes

A chemical process consists of the pretreatment of the substrates, the reaction, and the separation and purification of the product. The importance of separation technologies for the chemical production processes cannot be emphasized



highly enough. In chemical production, the separation processes require 43 % of the consumed energy and 40–70 % of the investment and running costs.<sup>[61]</sup> Therefore, its optimization is of utmost importance. The chemical process should be developed in such a way that separation processes are either not necessary at all or that they are simple and require as low an amount of energy as possible. One solution is to couple the reaction and separation, as is the case in reactive distillation and in absorption, adsorption, and membrane reactors.

In contrast to the classical chemical plant, reactive rectification is characterized by the combination of reaction and rectification in one apparatus unit. Conversions far above the equilibrium conversion (in an ideal case 100 %) and significantly higher selectivities can be reached by the direct rectificative removal of the products from the reaction zone. In the ideal case, further processing steps and recirculating flows are no longer necessary.<sup>[62]</sup> The heterogeneously catalyzed reactive rectification, for example, of methyl acetate is especially advantageous, since here the separation of the catalyst does not apply.<sup>[63]</sup> For all other separation methods, for example, adsorption, crystallization, extraction, membrane procedures, and ion exchange, essential improvements are necessary to achieve a 30 % reduction in material and energy consumption, water consumption, and emissions that are toxic to humans and the ecosystem by the year 2020.<sup>[61]</sup>

### 3. Products of the Chemical Industry

The products of the chemical industry display a great chemical diversity. Agenda 21 assumes there are approximately 100 000 chemical substances on the market worldwide. Approximately 1500 compounds make up about 95 % of the total world production. (Agenda 21, Chapter 19.11). The challenge for chemistry is to realize the manifold and different product characteristics of the mass products of the chemical industry with as few chemical base products as possible. An effective and large-scale recycling ought to be feasible and economic with only a few base products. The numerous fine and special chemicals have to become more effective, that is, the desired effect needs to be achieved with significantly lower amounts of substance. They need to be mineralized quickly when emitted into the environment. After all, it has to be possible to process chemical industry products in an environmentally benign way.

#### 3.1. Enlarging Chemical Product Diversity and Reducing Compound Diversity Simultaneously

At present, a great number of chemically different monomers are used for the synthesis of plastics in order to obtain the necessary material characteristics. This makes the effective recycling of plastics very difficult. Moreover, there are a number of monomers, for example, isocyanates, ethylene- and propyleneglycol, and acrylates, used for the synthesis of bulk plastics that rank comparably highly in the value-adding chain. The generation of a large variety of material characteristics from as few monomers as possible by a specific and new

coupling, as well as by the combination of polymers with themselves as well as with other materials, such as natural fibres, would be an important contribution to sustainable development.<sup>[64]</sup>

The polymerization of olefins, especially of ethene and propene, with organometallic catalysts has over the last few years developed into one of the largest industrial processes in the chemical industry. Approximately 66 million tons of polyolefins—polyethylene, polypropylene, copolymers, and polydienes—were produced worldwide in 1997. This value amounts to about 44 % of the total production of plastics, and is rising sharply: In 1990, it was still 43 million tons (corresponding to 43 %) and in 2005 it will probably be 100 million tons of polyolefins (corresponding to 45 % of the total production of plastics). The reasons for this development are clear. The new metallocene catalysts have opened up the possibility of varying the structure of polymers and their characteristics considerably.<sup>[65]</sup> Moreover, they make a detailed understanding of the mechanism and the stereochemistry of the polymerization of olefins possible.<sup>[66–69]</sup> By using metallocene catalysts, plastics can be made for the first time whereby their characteristic profile of properties, such as temperature resistance, hardness, shock resistance, and transparency, are precisely and largely controllable.<sup>[70]</sup>

Such new polyolefins could eventually substitute plastics derived from monomers, which are produced with higher resource usage and are less ecologically benign. One example is polyvinyl chloride (PVC) which is increasingly being queried socially, since it is produced from a toxic monomer and contains a large amount of plasticizers which can be washed out. Toxic waste is produced during its production and its disposal causes problems since hydrogen chloride is produced during combustion.<sup>[8c]</sup> PVC is now gradually being substituted by polyolefins. This is also the case with other special plastics, for example, polycarbonates, polyaziridines, and polyimides, the production of which requires a high amount of material and energy.<sup>[65]</sup>

#### 3.2. Product Design<sup>[17]</sup>

The protection of water resources, of water quality, and aquatic ecosystems is of highest priority for sustainable development (Agenda 21, Chapter 18). Chemical compounds, which as a result of their product characteristics enter the aquatic environment, should not endanger this environment and need to be biologically degradable. Persistent and semi-persistent chemicals must not be accumulated in any environmental compartment.<sup>[71]</sup> It is the challenge for chemistry to develop the molecules in such a way that they have the desired effect at a minimum dose, and that they are mineralized rapidly by the environment's naturally existing catabolic potential.<sup>[72]</sup> Here, the use of renewable raw materials, such as oils and fats,<sup>[49, 73]</sup> is especially important as are starch derivatives<sup>[47]</sup> in detergents, and oils and fats for lubricants.<sup>[74]</sup>

Water-soluble functional polymers and complexing agents are components of formulations used industrially as well as in the household. The homo- and copolymers of acrylic acid (Figure 3) currently used as sequestrants and dispersants as

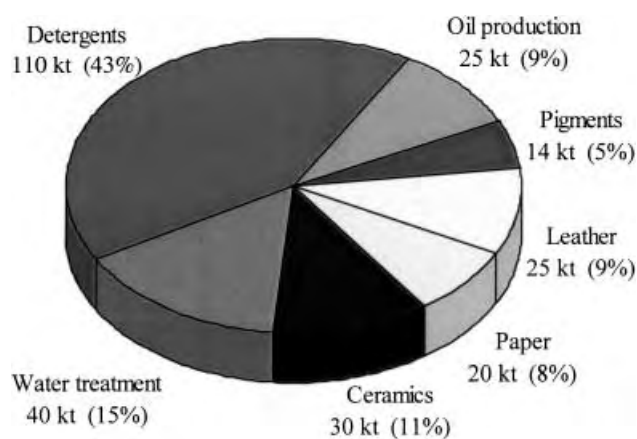


Figure 3. Areas of application of water-soluble polycarboxylates. The worldwide market volume is 265 000 t/a.<sup>[16b, 75]</sup>

well as the widely used complexing agent ethylenediaminetetraacetic acid (EDTA) are biologically not sufficiently degradable and, therefore, contamination of the surface waters cannot be excluded. Products which can be substituted for the polyacrylates are the biologically degradable polyaspartic acids, produced by means of thermal polymerization.<sup>[16d]</sup> Modern, biologically degradable complexing agents of the type of aminopolycarboxylic acids as, for example, iminodisuccinic acid (IDS) are possible alternatives to persistent complexing agents.<sup>[75]</sup>

### 3.3. Sustainable Processing of Chemical Products

The products of the chemical industry are mostly processed by the nonchemical industry into products for the end user. Organic solvents are very often used and are emitted as volatile organic chemicals (VOCs) into the atmosphere. In Germany these emissions amounted to  $1.197 \times 10^6$  t in 1988 and to  $1.090 \times 10^6$  t in 1995.<sup>[76]</sup> Similar data related to industrial production can be expected for the other industrialized countries. On the one hand this is an immense waste of resources and on the other hand this is a significant cause of the tropospheric ozone formation, which contributes to the summer smog. The politically determined ozone threshold value of  $110 \mu\text{g m}^{-3}$  as an environmental quality level requires that the emissions of organic compounds into the air have to decrease by 70–80% compared to the reference year (1988). For the Federal Republic of Germany this means: the total emission of VOCs including that from traffic has to be reduced from  $3.241 \times 10^6$  t in 1988 to  $650\text{--}950 \times 10^3$  t by the year 2007. The reductions in emission already achieved by the introduction of compulsory catalytic converters for exhaust gas, as regulated by traffic laws, now suggest that the use of solvents mainly in the processing industry makes up more than half of the total emissions. The main emissions are caused in coating, printing inks, and adhesive processing. (Figure 4). The development of chemical products which can be processed without the use and emission of VOCs in areas including those mentioned in Figure 4 is by no means trivial, but is a great challenge to chemistry. More success in this field

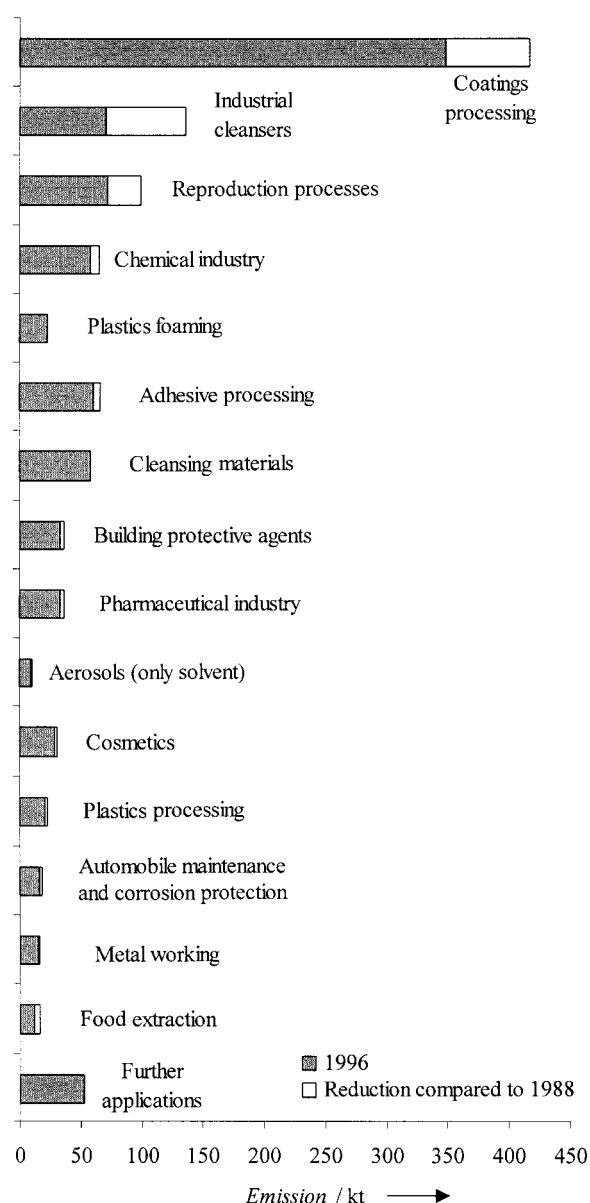


Figure 4. Emission of VOCs in Germany from the use of solvents in different industry segments (1988:  $1.197 \times 10^6$  t/a; 1995:  $1.09 \times 10^6$  t/a). The VOC emissions have to be reduced to 650 kt/a by the year 2007.<sup>[76]</sup>

would mean an important contribution to sustainable development. This contribution would be even more vital if these products from renewable raw materials could be produced ecologically benign and could be disposed of without problems.<sup>[77]</sup> In a case where a solvent is absolutely necessary, fluid or supercritical  $\text{CO}_2$  may be a substantial tool for the solution of environmental problems.<sup>[78]</sup>

The following steps are currently taken for the reduction of the VOC emissions in the development of new coating systems:<sup>[79, 80]</sup>

- binders are used with an essentially higher content of solid matter dissolved in organic solvents (high-solid coatings);
- water-diluted coatings that have a remaining content of organic solvents are used;
- powder coatings are used without solvents but frequently with organic cleavage products formed during the curing process;

d) radiation-hardening coating systems are used which to a large extent are free from solvents and even during the hardening do not develop any organic cleavage products. Binders based on oils and fats seem to be very promising for the development of solvent-free coatings.<sup>[81]</sup>

#### 4. Assessment of the Contribution of Chemical Process and Product Innovations to a Sustainable Development

Agenda 21 calls for “criteria and methodologies for the assessment of environmental impacts and resource requirements throughout the full life cycle of products and processes” (Chapter 4.20), and in numerous chapters it formulates the aims and measures necessary for chemistry to make an important contribution. These aims and measures have to be considered for an assessment of chemical processes and products in regard to their contribution to a sustainable development. There are three dimensions that generally need to be considered in an integrated way:

- an economic dimension
- a social dimension
- an ecological dimension

If the state of the operationalization is to be considered in regard to the economic and social dimension, then they are still at the very beginning.<sup>[9]</sup> The economic dimension is normally equated with the microeconomic success of the firms in question, the macroeconomic sustainability criteria are only formulated in single cases. For the social dimension, there are single indicator sets; however, they are only consistent to a certain extent. In contrast, the ecological dimension is extensively operationally defined.

##### 4.1. The Ecological Dimension

The ecological dimension of chemistry's contribution to sustainable development and its assessment has two sides:

1. The stress on the environment and consequently on the population by chemical production and its emissions as well as by chemical substances that are emitted into the environment for useful purposes but which also have negative effects.<sup>[82]</sup>
2. The more efficient exploitation of the resources by new chemical processes and new products in order to create conditions so that nine billion people can live in human dignity on earth.

##### 4.1.1. Environmentally Friendly Handling of Chemicals

Chapter 19 of Agenda 21 takes up the chemistry discussion of the last 30 years and comes to a final conclusion. However, many details need to be clarified. It contains detailed orders for action pertaining to the sustainable handling of toxic, that is, dangerous, chemicals and calls for a worldwide harmonization of classification and labeling of chemicals by the year 2000. Its implementation by state regulations will bring about

on a national, European, and international level a complete set of compound records, safety guidelines, safety data sheets, and poison characteristics of all chemicals used. The implementation of Chapter 19 was summarized by Hildebrandt and Schlottmann.<sup>[10]</sup> The program areas outlined in Chapter 19 refer to single-compound assessments. With regard to human toxicity, however, toxicological data of preparations and formulations ought to be recorded as well. This process would help to decide whether a single-compound treatment in the mixture represents a sufficient basis for a sustainable health protection or whether specific combinatory effects have to be considered as well.<sup>[83]</sup> The leading principles concerning this subject in the Responsible Care Initiative are as follows: “to provide chemicals that can be manufactured, transported, used and disposed of safely.”<sup>[11]</sup>

##### 4.1.2. Approaches to the Assessment of the Sustainability of Chemical Processes

The process parameters of established processes are (internally) known and can be used for the quantification of the use of resources, gross energy requirements (GER), waste, emissions, and related costs per product unit. A number of metrics have been developed which are used for assessment in the chemical industry.<sup>[84]</sup> As an example, the GER was compared for the two propylene oxide processes currently performed. Surprisingly, it was about the same for both processes at  $104 \text{ GJ t}^{-1}$  of propylene oxide.<sup>[23c]</sup> Further criteria such as waste, investments, expected profit, and social acceptance need to be included to enable a sound decision to be made. After consideration of all aspects, the oxirane process with styrene as a coupled product has clearly succeeded in taking over the top rank when it comes to new investments, relative to the chlorohydrin process. In Europe, the social discussion on “chlorine chemistry” was most probably decisive for this outcome.

The GER is accessible for a number of processes carried out at present to produce important organic base chemicals and intermediates (Figure 5); for example, it is approximately  $40 \text{ GJ t}^{-1}$  for acetaldehyde,  $80 \text{ GJ t}^{-1}$  for adipic acid, and  $104 \text{ GJ t}^{-1}$  for propylene oxide;<sup>[23a,b]</sup> Vegetable oils such as rape seed oil and linseed oil require a GER of approximately  $20 \text{ GJ t}^{-1}$ .<sup>[23a,b, 85]</sup> Here, the differences in the resource consumption are so high that it can be assumed that products based on vegetable oils could clearly be more environmentally benign than petrochemical products. Significantly different values for the GER is also evident in important bulk plastics (Figure 6). For example, the GER for one ton of epoxy resin is  $107 \text{ GJ t}^{-1}$ , which is almost twice as high as it is for alkyd resins at  $64 \text{ GJ t}^{-1}$  because the latter contains a portion of renewable raw materials. Remarkably, PVC has the lowest GER of  $53 \text{ GJ t}^{-1}$ , which is clearly lower than that for polyethylene at  $65 \text{ GJ t}^{-1}$ . However, the process energy for PVC at  $32 \text{ GJ t}^{-1}$  is 50% higher than for polyethylene at  $21 \text{ GJ t}^{-1}$ . The chemical energy accumulated in PVC at  $20 \text{ GJ t}^{-1}$ , however, is less than half that of polyethylene ( $43 \text{ GJ t}^{-1}$ ) because of the high chlorine content in the former. The GER, in relation to the process energy and the chemical

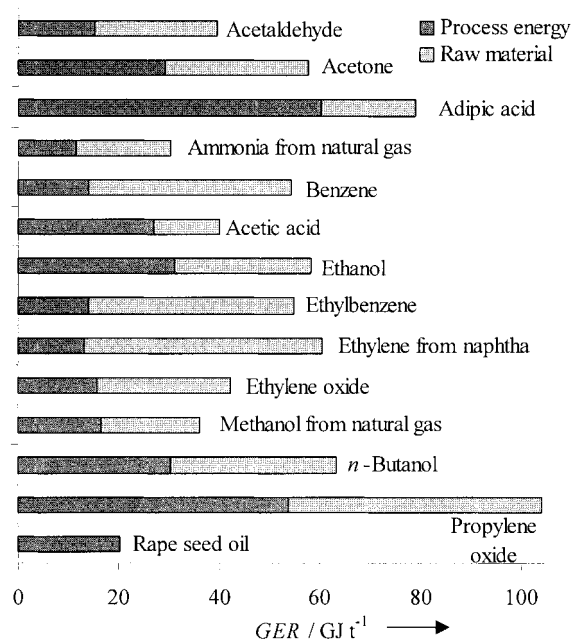


Figure 5. Gross energy requirements (GER) for important base chemicals.<sup>[22, 23c]</sup>

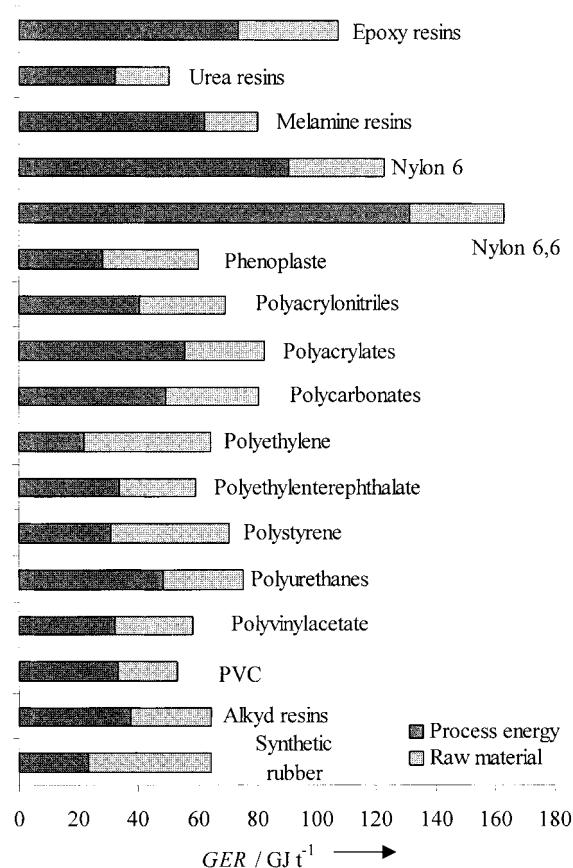


Figure 6. Gross energy requirements (GER) for important bulk plastics.<sup>[22, 23c]</sup>

energy accumulated in the product, is a useful measure for the assessment of bulk products.

A simple method for a quantitative comparison of the use of resources and environmental impact in syntheses of fine

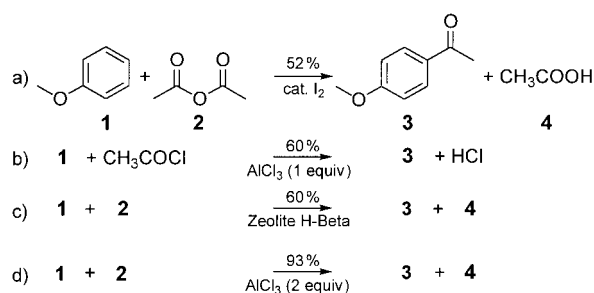
chemicals and pharmaceuticals at the earliest possible stage of process design,<sup>[86a]</sup> preferably already at the laboratory stage,<sup>[86b]</sup> is essential for the precise development of sustainable processes. Some approaches have been presented during the last few years.<sup>[87]</sup> We mainly follow Sheldon's proposal<sup>[88]</sup> which weights the environmental factor  $E$  (mass of waste, that is all compounds used which are not incorporated in the product, per mass unit of product) of a process with substance-specific weighting factors  $Q_{\text{output}}$ .<sup>[89]</sup> In this way, an environmental index<sup>[87a]</sup>  $EI_{\text{out}}$  of the waste is obtained for a process, the value of which reflects the potential environmental impact based on the mass of the product ( $\text{PEI kg}^{-1}$ ).<sup>[87f]</sup> Correspondingly, the mass index  $S^{-1}$  is weighted with  $Q_{\text{input}}$  to obtain the environmental index  $EI_{\text{in}}$ , which quantifies the potential environmental impact by the raw materials used (substrates, solvents, catalysts, auxiliary materials for the reaction and work-up procedure; Table 1). The weighting factor  $Q_{\text{input}}$

Table 1. Metrics applied to chemical syntheses for the assessment of resource requirement and potential environmental impact.

| Metrics                                                                                                  | Unit                          |
|----------------------------------------------------------------------------------------------------------|-------------------------------|
| mass index $S^{-1} = \frac{\sum \text{raw materials [kg]}}{\text{product [kg]}}$                         | [kg per kg]                   |
| environmental factor $E = \frac{\sum \text{waste [kg]}}{\text{product [kg]}}$                            | [kg per kg]                   |
| substance-specific potential environmental impact $Q_{\text{input}}^{[d]}$ and $Q_{\text{output}}^{[d]}$ | [PEI per kg] <sup>[a,b]</sup> |
| environmental index $EI_{\text{in}} = Q_{\text{input}} S^{-1}$                                           | [PEI per kg] <sup>[a,c]</sup> |
| environmental index $EI_{\text{out}} = Q_{\text{output}} E$                                              | [PEI per kg] <sup>[a,c]</sup> |

[a] PEI = potential environmental impact.<sup>[87f]</sup> [b] Refers to one kilogram of substance. [c] Refers to one kilogram of product. [d]  $1 \leq Q \leq 10$ .

considers the resources used, as well as the aspects of occupational safety and health, while  $Q_{\text{output}}$  essentially considers the human toxicity and ecotoxicity.<sup>[89b]</sup> As an example, these metrics were determined both fast and simply for four different laboratory syntheses of 4-methoxyacetophenone (Scheme 6) by using the software "EATOS" (Environmental Assessment Tool for Organic Syntheses<sup>[89a]</sup> (Figure 7). The zeolite-catalyzed Friedel–Crafts acylation requires the lowest material input, and therefore has the lowest mass index  $S^{-1}$  and correspondingly the lowest environmental factor  $E$ . The environmental indices  $EI_{\text{in}}$  and  $EI_{\text{out}}$  are also about one order of magnitude lower than in the other syntheses. Clearly, this synthesis of 4-methoxyacetophenone



Scheme 6. Different syntheses of 4-methoxyacetophenone from the same substrate with different acylation agents, solvents, and catalysts.

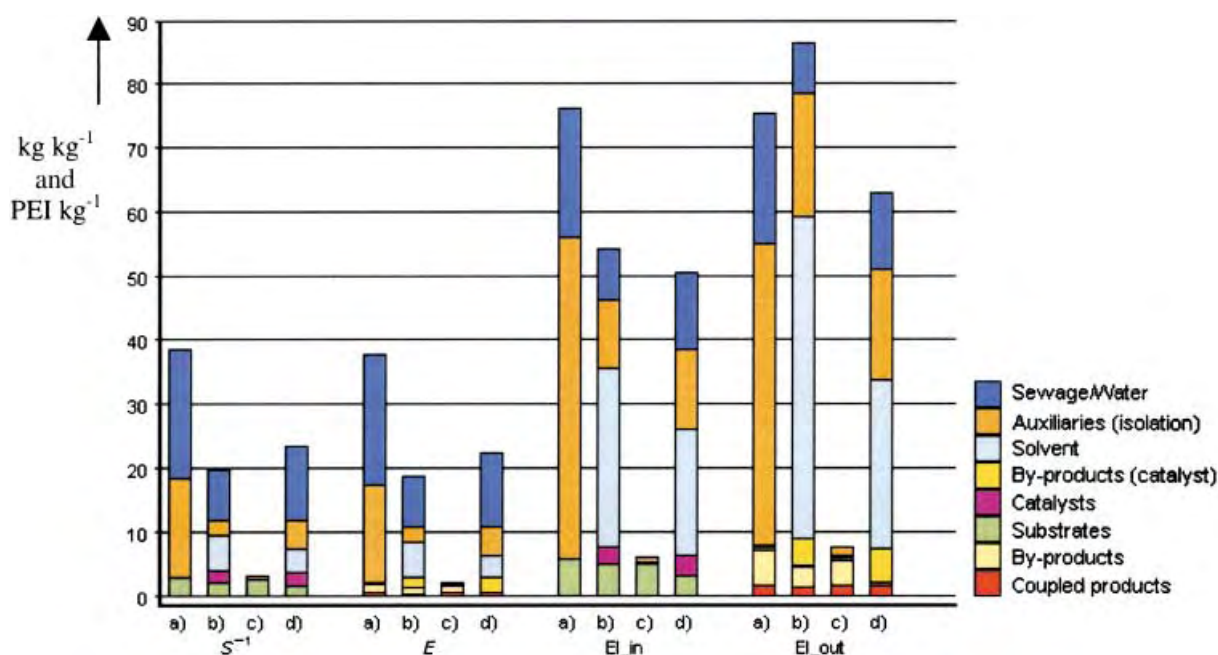


Figure 7. Assessment of syntheses of 4-methoxyacetophenone (Scheme 6) by means of the software EATOS: mass index  $S^{-1}$ , environmental factor  $E$ , environmental indices for input  $EI_{in}$  and output  $EI_{out}$  (see Table 1).

stresses the environment the least and should, therefore, be the preferred one. It is remarkable that the yield, the chemist's most often used value for estimating the synthesis quality, is clearly lower for synthesis c) than for synthesis d) and comparable to syntheses a) and b) (Scheme 6). Analysis by EATOS permits a detailed balancing of the reaction, a balancing that includes solvents, catalysts, by-products as well as auxiliary materials used during the work-up procedure. From this, it can clearly be seen, that reaction a) requires a costly work-up procedure while reactions b) and d) require solvents during reaction and work-up procedure that contribute decisively to the high resource requirements and the high potential environmental impact.

A system of building blocks with modules for the most important process chains that allows both the resource requirements and environmental impact on production of base chemicals, intermediates, and end products to be covered quantitatively by means of metrics that refer to a consistent basis data set would be extremely useful for an assessment of syntheses or processes, but unfortunately it is not yet available.

#### 4.1.3. Life-Cycle Assessment (LCA)

A life-cycle assessment<sup>[90]</sup> of a product is drawn from the "cradle to the grave", that is, from the extraction of raw materials to waste disposal or recycling. A life-cycle assessment consists of the goal and scope definition, inventory analysis, impact assessment, and interpretation. These proceedings are described in the ISO EN DIN 14040-43.<sup>[91]</sup> Azapagic and Clift have written an overview on the application of the LCA method for process optimization.<sup>[92]</sup> Life-cycle assessments were thus set up for bulk plastics.<sup>[93]</sup>

Leading surfactant and detergent producers compared the production of fat alcohol sulfate on the basis of renewable raw

materials with the petrochemical production in a life-cycle assessment.<sup>[87e, 94]</sup> There, it was stated that resource and energy consumption and emissions for the surfactant based on palm oil were clearly more favorable than for the one being produced from fossil feedstock. The comparison of UV-curable coatings, with linseed oil epoxide as a binder, to a binder produced on a petrochemical basis has shown clear advantages for the renewable raw material linseed oil. The gross energy requirements as well as the  $CO_2$  and  $NO_x$  emissions are almost one order of magnitude smaller when linseed oil epoxide was used. It is remarkable that during the production of the petrochemically derived binder, propylene oxide contributes more than half of the environmental impact (Figure 8).<sup>[85]</sup>

Life-cycle assessments were also set up for some biotechnological processes.<sup>[57]</sup> It is remarkable that bio-ethanol (world production 1991:  $15.1 \times 10^6$  t/a) has clear ecological advantages over synthetic ethanol ( $2.5 \times 10^6$  t/a). The demand for fossil primary energy for the latter amounts to  $62.3 \text{ MJ kg}^{-1}$ , but only to  $4.8 \text{ MJ kg}^{-1}$  for ethanol derived from sugar cane and  $19.1 \text{ MJ kg}^{-1}$  for ethanol from sugar beet. The  $CO_2$  emissions for synthetic ethanol amount to  $1.88 \text{ kg kg}^{-1}$ , while the  $CO_2$  emissions are credited for bioethanol.

#### 4.2. Measuring Economic-Ecological Efficiency

Economic-ecological parameters result from the micro-economic imperative on efficiency to achieve either a predefined environmental relief with as little financial effort as possible or a maximum environmental relief with a fixed financial sum. Therefore, simple measurements of economic-ecological efficiency link concrete single-environmental relief measures to microeconomic parameters:<sup>[92, 95]</sup> examples are the amount of reduction of  $SO_2$  per investment volume in

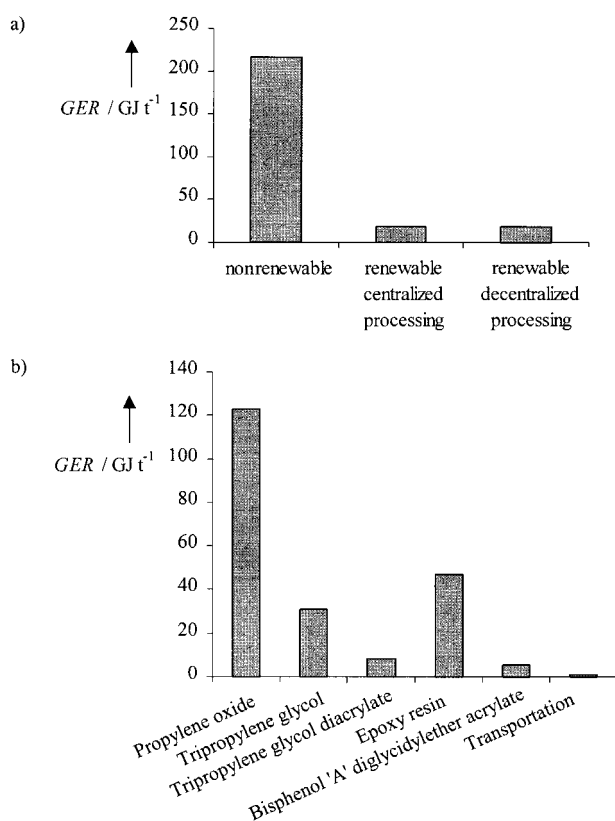


Figure 8. Comparison of the gross energy requirements (GER) for the production of a) a petrochemical (tripropylene glycol diacrylate/bisphenol A diglycidether acrylate 1/1) and of a renewable binder (linseed epoxide, centralized and decentralized processing of linseed); b) the compounds of the petrochemical binder. Similar relationships exist for  $\text{CO}_2$  and  $\text{NO}_x$  emissions.<sup>[85]</sup>

filters, costs per reduced kilogram of waste material, and turnover in Euro per energy consumption in kWh. Today, such environmental metrics parameters have largely been implemented in chemical firms, since they are also readily applicable.<sup>[95b]</sup> Evaluation is more difficult if product performance or even the total enterprise performance is to be assessed by means of an economic-ecological measure of efficiency. If, for example, three product alternatives (for example, for a dye) have to be estimated from the perspective of economic-ecological efficiency, the development expenditure or the increased production costs have to be contrasted with the total ecological relief. This is the point at which the aggregation problem which is well-known from the life-cycle assessment (for example, the trade-off between lower production of waste materials and higher energy consumption) comes in. In 1991, Schaltegger and Sturm presented the first comprehensive approach for such an aggregated ecological efficiency evaluation.<sup>[96]</sup> They based their report on the Swiss eco-point system and they chose the net contribution of product variants as a means of evaluation. In this way, they were able to calculate an aggregated economic-ecological efficiency value.

This economic-ecological efficiency evaluation has been slow to win recognition in Germany, mainly because the underlying eco-point aggregation methodology has not reached any consensus. Only recently have efforts been

undertaken by firms to take up the concept introduced by Schaltegger and Sturm, for example, the eco-efficiency analysis by BASF and the eco-check "Product excellence" by Bayer.<sup>[97]</sup>

### 4.3. Concepts Incorporating Sociopolitical Assessment Dimensions

Against the background of the sustainability postulate, the sociopolitical evaluation of innovative chemical processes and products has to orientate itself by criteria aimed at achieving a long-term social acceptability of the planned innovations. This comprises measures such as the reduction of risk potentials, health protection, the number and quality of jobs which are raised or lowered in the process, increased intra-generational and inter-generational social justice, broad acceptance, and compatibility with democracy. Naturally, balancing these criteria with the other dimensions of sustainability, which represent ecological and economic demands, is an endeavor that is not free from conflicting interests; a redefinition is required for every single case.

Therefore, concepts that evaluate chemical-political innovations for their social compatibility also have to consider the other dimensions of sustainability as early as possible in their initial stages so as to avoid developments in the wrong direction. This approach calls for evaluation concepts which, as the Enquete Commission of the German Bundestag on "Schutz der Umwelt und des Menschen" stated in its final report, cannot be decreed, but must be worked out by considering the various interests arising in a discursive process that includes a high number of participants.<sup>[9b]</sup> In this way, the sustainability postulate will, although it claims to be normative, become a concept of social orientation aimed at cooperation and the balance of interests.

Since the meaningfulness of cost-benefit analyses and risk analyses is only limited in regard to an estimation of the social consequences of the sustainability of chemical innovations, scenario analyses would probably provide the most suitable basis for evaluation since they display alternative development paths based on a collection and integrated processing of data. The most prominent advantage of the scenario analysis is that it presents future fields and their scopes for complex design, thus allowing an identification of synergies and potential conflicts. They might—perhaps in a discursive process—be suitable for an evaluation by means of ecological, economical, and social indicators.<sup>[92]</sup> The interests of the different parties involved might be considered in its formulation and moreover, the political options, which can be rated enforceable, could be shown more clearly. Such concepts have been successfully applied in a number of studies dealing with the complex consequences of social innovations.<sup>[98]</sup>

The first attempts have been made to create feasible operational systems which balance potential actions. There are two major examples of this: the concept "Who needs it",<sup>[99]</sup> developed in the cooperation of Dow Chemical with the London Sustainability Agency "Sustainability" which covers those fields in which chemical products are used and determines to what extent the needs arising in these fields

can be generalized. The concept does not qualitatively assess single products, but allows firms to identify suitable or critical fields of need in a fairly early stage and to adapt decisions on the product portfolio to sustainable development requirements. The instrument PROSA<sup>[100]</sup> developed in a cooperation between the Öko-Institut, (eco-institute) and Hoechst AG is heading for a similar direction. By means of this tool different product alternatives are evaluated for sustainability (in the pilot project, for example, roof material made from plastics and preserving agents were used), not only by applying various individual ecological parameters, but also in the context of their application fields (Germany versus China).

## 5. Organization and Innovation

Process and product innovations are the results of the creative thinking and actions of humans within organizations. This also applies to ecological innovations. However, businesses and chemical sub-branches widely differ with respect to their innovation potential.<sup>[101]</sup> Research on organizations has shown that a number of factors have an impact on the development of process and product innovations. These factors are summarized under the term of “innovation system”<sup>[102]</sup> (Figure 9). In addition to political and legal frame

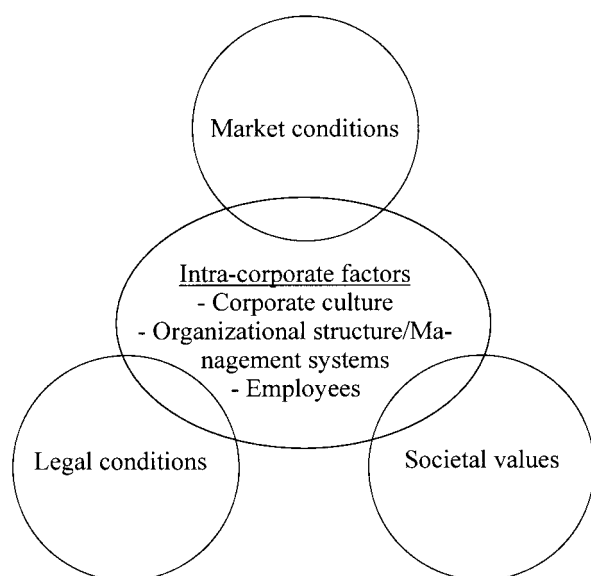


Figure 9. Factors that influence the innovation performance of companies.

conditions (Section 6) as well as societal concepts and values, the term also comprises the marketing conditions (customer demand for ecologically optimized products and competitive pressure arising from the ecological product innovations of competitors) and internal company factors. Empirical studies have shown that the majority of chemical innovations were basically generated by committed key personalities within companies.<sup>[103]</sup> The following section focuses on internal factors that can be influenced by companies. Such factors have so far been treated in papers on innovation management in the chemical industry, on corporate environmental inno-

vation in general, as well as on environmental innovation in the chemical industry in particular. This section focuses on the latter subject area. However, only a limited number of empirical studies on this topic have so far been published.<sup>[104]</sup> Hence, transfers from the two other subject areas also need to be considered for statements regarding the conditions for promoting ecological innovation in the chemical industry.

Research and development (R&D) processes are characterized by high risks and enormous capital needs. They also require interdisciplinary cooperation, particularly at the interfaces.<sup>[105]</sup> As a consequence, the number of company cooperations aimed at incorporating external knowledge into R&D processes rises. This not only applies to company cooperations between customers and suppliers, but also between competitors in the framework of R&D alliances, as well as—to a rising degree—to cooperations between external interest groups (for example, environmental protection groups). It is precisely these groups that have turned out to be the driving force behind the promotion of sustainable process and product innovation.<sup>[106]</sup> At the same time, a trend towards company mergers and a concomitant orientation towards specialized product areas has been observed, particularly in research-intensive sections of the chemical industry.<sup>[103]</sup>

It is revealing to link these general features of innovations to research on corporate environmental innovation. In this way it becomes clear how the general conditions of the market and of companies affect the environmental innovation behavior of companies (Table 2).<sup>[107]</sup>

Table 2. Factors determining corporate environmental innovations. The major variables established in an empirical study by Lee are shown.<sup>[107]</sup>

| Market/company characteristics                   | Influence on the innovation activities                                                      |
|--------------------------------------------------|---------------------------------------------------------------------------------------------|
| size of company                                  | higher formalization of innovation processes in big companies, no better innovation results |
| type of industry                                 | no significant differences between producers of consumer and industrial goods               |
| growth rate                                      | positive correlation with risky innovation, no correlation with environmental innovation    |
| intensity of competition                         | price competition influences innovations in the direction of cost savings                   |
| attractiveness of markets (size and growth rate) | attractive markets only foster innovation activities in general                             |

Accordingly, the branch concentrations (that is, the relatively increased importance of major companies in this sector)<sup>[108]</sup> which have been observed in the chemical industry and which were among other things triggered by R&D dynamics<sup>[108]</sup> do not necessarily lead to a greater success in environmentally related innovation. Although environmental protection is more formalized in bigger companies, this does not automatically correlate with successful environmental process and product innovations. The highly intense competition that has been observed in many chemical sub-branches promotes cost-saving innovations.<sup>[109]</sup> This opens up opportunities for innovations in environmental processes that are accompanied by cost savings in the production process (low-energy consumption or low amounts of waste, higher yields,



etc.). In rapidly growing markets (for example, pharmaceuticals, specific areas of specialized chemistry), the general conditions for successful product innovation are also improving, however, not necessarily towards environmental innovations.

Studies on chemical innovations and on corporate environmental innovations clearly show that the emergence of innovations in environmental processes and products cannot only be attributed to external factors, but was promoted considerably by company-specific factors,<sup>[110]</sup> namely factors such as the company culture, company management,<sup>[111]</sup> and the respective R&D policies pursued. This finding corresponds to the results of the few relevant empirical data available so far on the environmental innovation behavior in the chemical industry.<sup>[104,112]</sup> In his studies of the chemical industry Kreikebaum, for example, identified “long-term planning horizons, capable and motivated staff, interdisciplinary R&D working groups,<sup>[113]</sup> unhindered communication within the company, involvement of external people in new product developments, and an ecologically oriented R&D management” as company-specific factors that promote successful environmental innovations.

Studies on the correlations between stock and environmental performance in the chemical industry stress the importance of an orientation towards sustainability for ecologically and economically successful innovations.<sup>[114]</sup> More recent studies have revealed the importance of “soft” factors, of cooperations,<sup>[115]</sup> and of a supply-chain management that is supported by suitable cost-accounting systems<sup>[116]</sup> for successful environmental innovations.

A promising strategy that can be pursued with respect to basic innovations is to break up central concern structures in favor of cooperations with small innovative companies: Empirical studies on the plastics industry have shown that basic innovations are frequently generated by “outsiders”, namely, by individuals or companies which only play a marginal role in a branch. By contrast, major companies are more predestined to organize incremental innovations efficiently.<sup>[117]</sup> It is essential to also consider these findings in environment-oriented process and product innovations, for example, by closely cooperating with innovative biotech start-up companies in the field of ecologically oriented process improvements,<sup>[118]</sup> by involving researchers with unconventional ways of working and thinking in development processes, and by an open communication climate.

“Soft” factors for innovations cannot be controlled directly, but organizational conditions can be created under which they can develop easily. In this context, industrial models and visions (such as those realized particularly in the US chemical industry<sup>[13]</sup> but which are also part of the Responsible Care Program<sup>[11]</sup>) as well as company-specific visions (such as the zero-waste philosophies of many US companies, for example, Monsanto and DuPont) play a major role. At the management level, such models are needed to focus strategic programs on specific goals. An illustrative example of this is the “Verbund” vision of BASF AG<sup>[119]</sup> which promotes thinking in terms of integrated synergies not only with respect to production processes (efficient use of raw materials, energy, and intermediates, re-use by-products and residual materials, minimi-

zation of transportation of substances, etc.), but also promotes relationships between BASF and its suppliers, customers, and interest groups by following a common model.

### 5.1. Cooperations

Cooperations have become a key factor of environmental innovation in the chemical industry. They not only play a crucial role in the innovation process itself, which should include as much external knowledge as possible (see Section 5), but also in the implementation of innovations in value-added chains: It has become clear that many technically and economically impressive product innovations which, by ecological and economic standards, were marketed successfully by the various pioneer companies are slow to win recognition in the entire application branch.<sup>[120]</sup>

Most companies only have a limited innovation potential and a high level of persistency. In general, the innovation-readiness of the persons involved is overestimated. The limited innovation potential not only shows itself through key personalities in companies but also by suppliers and the institutes counseling the companies. In particular, innovations are rejected for being too risky if a company is in a difficult economic situation. The same is true for companies working to capacity, who fear that changes in processes will jeopardize the smooth flow of production.<sup>[121]</sup> The time at which a substitution can be made always seems to be wrong.

The proportion of innovative and flexible companies which are ready to implement environmental innovation is rather small in the branches. Lissner's<sup>[122]</sup> estimate of their share ranges from 1–20%, depending on the branch. It is crucial for the diffusion of more sustainable chemicals that companies operate successfully in this field. If this success turns out to be lasting, this will get around, thus encouraging follow-up companies to make substitutions. Nonetheless, the pioneer companies take great risks (for example, because plant and machine makers disclaim liability if new, environmentally friendly tools/operational procedures are applied). The importance of interorganizational cooperation for a sustainable development also arises from other considerations: Most chemical products are incorporated in product systems, that is, are not used in an isolated manner. The use of plastics in automobile production to reduce weight is a good example of this (such as for the development of the “3-liter car” which uses 3 liters of fuel to travel 100 km). Substitution of the currently used material with plastics can only be achieved through a close cooperation between producers and customers and, possibly, standardization panels to ensure that the substitute not only has the appropriate properties (for example, shock resistance, durability) but also meets all legal norms and quality standards beyond this level.

## 6. An Innovation-Promoting Political Pattern for Sustainable Development

As a result of the 1992 Rio Declaration<sup>[1]</sup> and Agenda 21<sup>[7]</sup> the international and political efforts aimed at promoting a

sustainable development in chemistry have been considerably increased. Major requirements of Agenda 21 that need to be met by the chemical industry and political institutions center around an internationally agreed assessment of chemical risks, a harmonization of classification and labeling of chemicals, the exchange of information, the implementation of risk-reduction programs, and the creation of favorable conditions for an efficient management of hazardous material, particularly in Third-World countries. These requirements were to be met by establishing a number of international forums (Intergovernmental Forum on Chemical Safety, IFCS), programs (for example, International Program on Chemical Safety, IPCS), conventions (Prior Informed Consent, PIC), and by holding various follow-up conferences. These efforts gave rise to a wide international discussion on the safe management of chemicals. Significant progress has been made, at least as far as the assessment of risks involved and regulations to be introduced are concerned.<sup>[10]</sup>

In parallel with this development, the Responsible Care Program of the chemical industry<sup>[11]</sup> launched by Canada (1984) and the USA has in the meantime induced companies worldwide to voluntarily commit themselves to constantly upgrade and implement standards in the areas of safety, health care, and environmental protection, regardless of legal requirements. This has also been documented in reports issued by the chemical industry.<sup>[123]</sup> The chemical industry, particularly in the USA, has closely interlinked their efforts with governmental programs such as the "Green Chemistry Challenge". This federal program now also includes standards from the Responsible Care Program. The Research Ministry in Germany has stated that it intends to point the way by allocating research assignments on "Sustainable Chemistry".<sup>[124]</sup> The Responsible Care Program is currently being extended by social and economic elements of entrepreneurial responsibility, thus making it a self-obligation for the chemical industry to focus on sustainability in the steps they take.<sup>[14, 125a]</sup>

If the chemical industry is to make a substantial contribution to a worldwide sustainable development it needs to go beyond the current level of safety regulations and risk reduction that exist in this sector. On the one hand, the quantities of chemicals used must be reduced in order to save resources and energy, and on the other hand, the search for lower risk substances must be pushed ahead in order to make it possible to avoid the use of high-risk chemicals outside of chemical production processes. This can be achieved by making sure as early as possible in the development of base chemicals and in the product design<sup>[17]</sup> that sustainability requirements are met when the substances are further processed. One of the demands made by Agenda 21 to governments to meet this goal was to coordinate their efforts with international organizations in charge and to "adopt policies and regulatory and non-regulatory measures to identify, and minimize exposure to, toxic chemicals by replacing them with less toxic substitutes and ultimately phasing out the chemicals that pose unreasonable and otherwise unmanageable risk to human health and the environment and those that are toxic, persistent and bio-accumulative and whose use cannot be adequately controlled" (Agenda 21, chapter 19.49c).<sup>[7]</sup> Measures that are con-

sidered effective in this context are: advancing environmentally friendly products and technologies, giving financial incentives, improving product labeling, and strengthening restrictions and prohibitions.

Numerous political concepts have been developed in recent years at the national, European, and international level to improve the political conditions for innovations. All the concepts have one feature in common: the realization that governmental control systems (command and control) need to be complemented by context-oriented bottom-up approaches which give more importance to procedural regulations, economic incentives, self-control, and the participation of social participants.

The most recent White Paper of the European Commission entitled "Strategy for a future Chemicals Policy", a preliminary version of a new integrated Chemicals Guideline, includes some elements of these political goals. In view of the precautionary principles and the EU guideline guaranteeing a high level of protection to human health and the environment, the "creation of incentives for substituting hazardous with less hazardous substances, where alternatives are available", is considered the overall objective to be achieved.<sup>[126]</sup> Experience has shown that the notification system currently in place impaired innovations in the development of new and safer substances. Instead, a strengthened liability law and a facilitated access to information on chemicals for consumers and the public could advance innovation in this field. Extending responsibility for the safety, disposal, and recycling of a product to suppliers is another possibility of boosting innovation. Changes in testing procedures which existing chemicals now also have to undergo may considerably boost the demand for substitute substances. With respect to these procedures, the Commission suggests to "raise the current threshold values for the notification and testing of new substances, to extend the conditions of deviations in research and development assignments and to allow a more flexible use and provision of test data".<sup>[126]</sup> Priorities in research need to be set at the national as well as at the EU level.<sup>[127]</sup>

Although the chemical industry in Europe agreed in principle to the basic objectives of the White Paper, it sharply criticized the practical measures which need to be taken as being too bureaucratic and counterproductive: "Of particular concern is the introduction of an 'Authorization' process that is based on the intrinsic properties of chemicals rather than on the real risks that they may pose. As a result decisions may be taken that increase the number of chemicals that are restricted or banned arbitrarily."<sup>[128]</sup> The output and mode of usage and not the intrinsic properties of chemicals should provide the basis for an assessment of risks. A compromise between the two controversial positions will probably be established during the process of bargaining on the directives which guarantees the necessary economic incentives for the substitution of hazardous substances, while taking into account the reservations about using too elaborate testing procedures on substances which are processed on a small scale.

The "Green Book on Integrated Product Policy"<sup>[129]</sup> published in March 2001 by the European Commission was

written to open up the markets for environmentally friendly products. In addition to this, it suggests that economic incentives should be offered and transparency created. An integrated product policy needs to center around decisive environmentally relevant stages in the life cycle of a product, that is, ecological design in which the “pollutant-pays-first” principle in establishing the product prices and enabling consumers to make an informed decision are considered. A mixture of instruments has been suggested to bring about the change: differentiated taxation, an extension of producer responsibility by EU legal regulations, introducing privileges in the public procurement system, extended product information, and developing standards for ecologically friendly design. In particular, however, the Green Book is expected to stimulate a public discussion of product policy and thus to generate a European strategy for product-related ecopolitical measures.

The discussion of chemicals legislation in the USA is also dominated by the heavy legal restrictions that are in place. These are the result of strict standards for cost-consumer trade-offs and of a stricter interpretation of the term “risk”. The American policy pursued in this field is also changing and now includes new innovation-oriented elements which give more importance to negotiation and coordination processes and which favor “softer” instruments that are based on willingness and mutuality. Accordingly, the procedure for licensing new substances in the USA comprises more flexible tests which vary according to the risks involved; by contrast, the block test procedures applied in the European Union are rather inflexible. These different licensing procedures has meant that companies in the USA had on average 425 new substances registered annually compared to 143 in the EU.<sup>[130]</sup> In general it can be stated that the environmental policy pursued by the US government in consensus with industry is more closely linked to a management approach in order to promote alternative substances.<sup>[131]</sup> In 1998 the US government, represented by the Environmental Defense Fund (EDF), reached an agreement with the Chemical Manufacturers Association (CMA) which states that within a 6-year period 2800 common chemicals with a high output (more than 500 t/a year) will be tested for their toxicity. According to CMA this ambitious program can only be completed if it is supported by chemical companies from all OECD member states.<sup>[132]</sup>

### 6.1. The Search for a Political Pattern Promoting Innovation

The new control policy pursued worldwide is aimed at reaching agreements at the negotiating table through consensus-building strategies and through revised decision-making principles that result from increased informative transparency. The rationality of these strategies is supported by the experience gained in the use of a political pattern that focused on bans and substance restriction. Only rarely are substitution processes generated as a result of bans on substances that are hazardous to health or to the environment. Such processes can only be sustained for an extended period of time through

major political efforts. The most recent example of this is the convention on banning the 12 most-persistent organic pollutants (POPs) that was reached on 23 May 2001.<sup>[133]</sup> However, this most important convention has not been ratified by the most important industrialized countries up until now. However, there are other bans, restrictions of use, and instructive and qualifying regulations which are widely opposed. Many practitioners prefer eluding existing regulations to searching for less-hazardous substitute substances.

A successful example, such as the International CFC Regime that resulted from the Montreal protocols of 1987, which stipulates a gradual strengthening of regulations shows how “the diffusion of new procedures can be achieved through minimal political cost if the achievement of objectives set by the state is supported by graded and flexible instrumentation which increases the obligation to adjust in a calculable way and only provides for mandatory restraints as a last resort.”<sup>[134]</sup> It appears that new forms of political regulation are required to promote sustainable innovations. To achieve this, a complex political pattern needs to be implemented in which state and nonstate participants unite their efforts (as has been called for in Agenda 21, chapter 23). Not only the course of the decision-making process and the individual measures taken are important in this context, but also the political style chosen, as well as the configuration of participants involved and the political-institutional context in which this process passes must be considered.

The international comparative environmental innovation research has in recent years developed determinants which make it possible to pursue a policy of sustainability on the basis of politically determined conditions. These determinants include: rapid circulation of environmental information, notification of new regulations or their strengthening in conjunction with graded and flexible instrumentation (“threat and control”), and a cooperative political style.<sup>[135]</sup> An innovation-promoting policy pattern needs to be pursued which meets the following requirements:

- innovation-friendly instruments which are based on strategic environmental planning and objectives need to be combined, economic incentives must be offered, and efforts to implement innovations need to be promoted in all stages.
- an innovation-friendly political style which is dialogic, consensus-oriented, calculable, ambitious, flexible, and management-oriented.
- a configuration of participants which promotes the political integration and networking of many stakeholders and institutions involved, leads to close ties between regulators and those regulated, involves major stakeholders in the dialogue, and interlinks those targeted by the policy.<sup>[136]</sup>

The international debate on sustainability in the chemical sector which started after the 1992 Rio summit has had two major consequences: Firstly, it generated a number of institutional provisions by which the risks involved in the handling of toxic chemicals were reduced and secondly this debate pushed the search for a political pattern by which a sustainable development in the chemical sector can be achieved through the interaction between central (supra)national and nonstate participants. Political networks have emerged during the process which seek to reach a consensus on the objectives to

be pursued and on the ways in which suitable political instruments can be combined; some success has already been achieved. It is anticipated that the substitution of unsustainable substances and mixtures is facilitated if “the ecological motivation and the provision of potential innovators with information is improved and above all if their investment risk is reduced by calculable provisions”.<sup>[137]</sup>

The first signs of such cooperation relationships emerged some years ago in some countries. In Germany, for example, the so-called “Chemiedialog”, in which representatives of the chemical industry, of the chemistry union, of environmental associations, and state officials participated, has helped to promote a cooperative political style which has paved the way for an innovation-friendly political climate despite existing conflicts of interests.<sup>[138]</sup> A political pattern that is most suitable for monitoring and promoting processes of innovation not only comprises regulatory measures and incentives from the state but also self-regulatory efforts undertaken by the chemical industry as well as a dialogue between the three participants involved, namely, the state, the chemical industry, and the general public, on the objectives to be achieved.

The responsibilities incumbent upon the state are: strategic environmental planning by drawing up national environmental plans including quantitative objectives to be achieved, institutionalized success control, and pursuing a differentiated target-group policy, which has already been implemented with considerable success, for example, in Sweden, Denmark, The Netherlands, and South Korea. EU regulations for the public sector nowadays allow for opening up the public procurement system to environmentally friendly products.<sup>[129b]</sup> It is also necessary to develop criteria for the allocation of funds to research in the sensitive area of product development and procedures applied. Application of these criteria makes it possible to assess if a research project promotes sustainability.

In addition to this, measures taken to improve the availability of information and to increase product transparency are gaining in importance: labeling requirements which also include life-cycle assessments (according to ISO 14021), awarding of environmental quality marks, and warnings issued by the state provide the consumer with practicable guidelines. The EU Green Book on an Integrated Product Policy suggests, in following the “new approach”,<sup>[17]</sup> that influence on the product design be exerted at an early stage. Manufacturers are expected to implement “harmonized norms” which are currently developed (by order of the EU commission) by standardization authorities that also take environmentally relevant features into account and ensure citizen participation in the procedure. If manufacturers applied these norms they could choose the way in which they prove that basic requirements were met and their products could be distributed freely within the European Single Market because they meet the relevant legal regulations.<sup>[129c]</sup>

Some self-regulatory measures have already been put to the test in the chemical industry. Voluntary branch agreements which have stimulated continued improvements of some technologies are already in place, such as the reduction of health-hazardous emissions. Positive experience has been gained in Denmark by setting up so-called “product panels” which are composed of manufacturers of a specific product

group who agreed to reduce the use of hazardous substances.<sup>[129d]</sup> It is well known in industry that self-obligations with respect to the reduction of ecologically harmful discharges within limited time periods already exist, however, permanent state control and sanctioning measures are needed to ensure that these obligations are met. Although environmental management systems which also include environmental screening (pursuant to EMAS II or ISO 14001) are not primarily aimed at products but at implementing controlled operational procedures and their continual improvement with respect to environmental sustainability, they nevertheless are of great importance in the gathering of data on the environmental impact of the respective production process. A political pattern in which state interference only increases gradually, would give industry the chance to release its self-regulatory powers, to get ready for the transition over an extended period of time, and to implement the transformation under economically justifiable conditions.

## 7. Summary and Outlook

The principles given in the 1992 Rio Declaration on Environment and Development and in Agenda 21 should provide the basis for the development of concepts on the contribution of chemistry to a sustainable development. Our review has been aimed at identifying the goals that need to be met by chemistry in fundamental as well as in applied research and we have given examples of chemical processes and products, particularly for organic chemistry. We have exemplified the outstanding role of catalysis—heterogeneous, homogeneous, enzymatic—with direct oxidations with oxygen, and we have pointed to the possibility of using renewable raw materials in the chemical industry. Furthermore we stressed the importance of optimizing separation operations to reduce energy consumption, with reactive rectification as an example. Polyolefins are an example of the challenge of obtaining the manifold and diverse product properties of the mass products of the chemical industry by using as few chemical elements as possible. The new metallocene catalysts open up an enormous range of possibilities to tailor the structure of polymers and hence to widely vary the material properties. Moreover the use of only a few base chemicals not only enables an effective, large-scale recovery, it is also reasonable in economic terms. The numerous fine and special chemicals must achieve the desired effect with significantly lower amounts of substance and the possibility of bioaccumulation must be excluded by molecule design as early as possible in the planning stage of the synthesis. After all, it must be possible to process the products of the chemical industry by applying environmentally friendly procedures, namely without VOC emissions.

Chemical process and product innovations per se don't contribute positively to a sustainable development. To achieve this an understanding of product and process innovations and their economic implications, their potential for political and social control, and their ecological effects is required, as is a comparative evaluation. The first signs of this have emerged and have been described. The ongoing

discussion of the Green Book of the EU Commission on integrated product policies shows the importance of such an integrated view. The issue of a "product responsibility" in the chemical sector can only be treated if the chemical properties of products and their application patterns are analyzed together with the possibilities of political control over individual product classes.

A critical stocktaking of the implementation of Agenda 21 needs to be done prior to the 2002 Rio + 10 Conference in Johannesburg. Some of the urgent questions raised in Agenda 21 have been addressed by chemistry as well as in science and industry, but so far no definite answers have been given. Hence, it is imperative to address these questions and to scientifically tackle those aspects that can be treated by chemistry in interdisciplinary cooperation. The five-level model used in the present review may serve as an example of this. A concept such as this should also be applied to teaching and become part of the chemistry curricula in school and universities.

### Rio Declaration—Selected Principles

**Principle 1:** Human beings are at the center of concerns for sustainable development. They are entitled to a healthy and productive life in harmony with nature.

**Principle 2:** States have, in accordance with the Charter of the United Nations and the principles of international law, the sovereign right to exploit their own resources pursuant to their own environmental and developmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction.

**Principle 3:** The right to development must be fulfilled so as to equitably meet developmental and environmental needs of present and future generations.

**Principle 4:** In order to achieve sustainable development, environmental protection shall constitute an integral part of the development process and cannot be considered in isolation from it.

**Principle 5:** All States and all people shall cooperate in the essential task of eradicating poverty as an indispensable requirement for sustainable development, in order to decrease the disparities in standards of living and better meet the needs of the majority of the people of the world.

**Principle 6:** The special situation and needs of developing countries, particularly the least developed and those most environmentally vulnerable, shall be given special priority. International actions in the field of environment and development should also address the interests and needs of all countries.

**Principle 7:** States shall cooperate in a spirit of global partnership to conserve, protect, and restore the health and integrity of the Earth's ecosystem. In view of the different contributions to global environmental degradation, States have common but differentiated responsibilities. The developed countries acknowledge the responsibility that they bear in the international pursuit of sustainable development in view of the pressures their societies place on the global

environment and of the technologies and financial resources they command.

**Principle 8:** To achieve sustainable development and a higher quality of life for all people, States should reduce and eliminate unsustainable patterns of production and consumption and promote appropriate demographic policies.

**Principle 9:** States should cooperate to strengthen endogenous capacity building for sustainable development by improving scientific understanding through exchanges of scientific and technological knowledge, and by enhancing the development, adaptation, diffusion, and transfer of technologies, including new and innovative technologies.

**Principle 11:** States shall enact effective environmental legislation. Environmental standards, management objectives, and priorities should reflect the environmental and developmental context to which they apply. Standards applied by some countries may be inappropriate and of unwarranted economic and social cost to other countries, in particular developing countries.

**Principle 14:** States should effectively cooperate to discourage or prevent the relocation and transfer to other States of any activities and substances that cause severe environmental degradation or are found to be harmful to human health.

**Principle 15:** In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

**Principle 16:** National authorities should endeavour to promote the internalization of environmental costs and the use of economic instruments, taking into account the approach that the polluter should, in principle, bear the cost of pollution, with due regard to the public interest and without distorting international trade and investment.

**Principle 17:** Environmental impact assessment, as a national instrument, shall be undertaken for proposed activities that are likely to have a significant adverse impact on the environment and are subject to a decision of a competent national authority.

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## Glossary

**Base chemicals:** Products of the chemical industry, manufactured globally at a scale of more than  $1 \times 10^6$  tons per year.

**Chemical biotechnology:** Application of biotechnology to produce chemicals.

**Economic-ecological efficiency:** Ratio of ecological improvement to economic input variable (for example, cost, profit reduction/reduction of the marginal return).

**End of the pipe environmental protection:** A term used to describe environmental measures taken after the occurrence of emissions in the widest sense (exhaust air, waste water, waste, noise, etc.).

**Gross energy requirements (GER):** GER indicate the total **primary energy** consumption of the entire process chain to manufacture a chemical product. The GER includes energetic consumption, which in chemical processes is largely the process energy, and non-energetic consumption, namely the direct, material use of fossil energy sources such as crude oil.

**Innovation system:** The term comprises external influencing factors (such as, framework conditions set by the state, market conditions, customer behavior) and internal company influencing factors which impact the innovation behavior of companies.

**Integrated environmental protection:** A term used for pollution-control measures which help to avoid ecologically harmful effects by selecting environmentally friendly substances, procedures, and technologies (production-integrated environmental protection) and for products which are developed in an effort to keep the burden on the

environment as small as possible during their life cycle (product-integrated environmental protection).

**Integrated product policy:** The concept of an integrated product policy is aimed at reducing the burden that products place on the environment during their life cycles—from the depletion of resources to waste disposal.

**Life-cycle assessment (LCA):** In life-cycle assessments the entire life cycle (product line) of a product (extraction and processing of raw materials, production, distribution and transport, use, consumption, and disposal) as well as the potential ecological effects are analyzed, and the material and energy conversions occurring in the life cycle and the resulting burden on the environment are assessed.

**Metrics:** Metrics such as mass index, environmental factor, and environmental indices are ratios which can be used as benchmarks for assessing phenomena such as chemical syntheses.

**Political pattern:** Contrary to another approach which only considers the question of instruments used, this term comprises the totality of the factors dominating the political decision-making process: the political-institutional context of action, the political style, the instruments used, and the relationship between the state and the target groups.

**Preventive environmental protection:** The term comprises all those measures which directly or indirectly help to avoid environmental damage or burdens (for example, product and production-integrated environmental protection, technology assessment).

**Primary energy:** A term used for energy sources, for example, crude

oil, mineral coal, natural gas, and uranium, in the state they are mined, namely, prior to conversion.

**Product panels:** Groups of companies, which join their efforts to determine how environmental goals can be achieved for their product group and how arising obstacles can be overcome.

**Resources:** In a narrower sense the term is used for natural capital, raw materials, energy sources, and environmental media, whereby a distinction can be made between (partly) renewable and nonrenewable resources.

**Responsible care:** Binding obligation of the chemical industry to self-responsibility in the areas of health, safety, and environment. The self-obligations are established in basic guidelines and are implemented by the national chemical associations.

**Sustainable development:** A term used to describe an environmental and development concept, which was formulated together with other papers in the Brundtland Report; at the 1992 UN Conference on Environment and Development in Rio de Janeiro the 27 principles of sustainable development were adopted and put in concrete terms in the working program of Agenda 21.

**Verbund:** Interplay between production processes and production plants as well as a close cooperation between businesses and customers, suppliers, and interest groups to achieve economic and ecological advantages.

**VOCs (volatile organic chemicals):** A large variety of substances which under intense solar radiation promote the formation of tropospheric ozone and hence of summer smog.

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# De Novo Structure Determination from Residual Dipolar Couplings by NMR Spectroscopy \*\*

Bernd Simon and Michael Sattler\*

NMR spectroscopy is, next to crystallography, the only method for determination of the high-resolution structure of biomacromolecules such as proteins, nucleic acids, and their complexes. NMR spectroscopy is unique in that it allows the study of the structure and dynamics of these molecules in solution. Until recently, solution structures determined by NMR spectroscopy were mainly based on distance restraints obtained from proton/proton nuclear Overhauser effects (NOEs). Hus et al. have now for the first time demonstrated that the backbone structure of a protein can be determined de novo from residual dipolar couplings (RDCs) without the use of NOE data.<sup>[1]</sup> This achievement represents a considerable milestone in the rapidly growing applications of residual dipolar couplings for the elucidation of biomolecular structures as outlined below.

The main source of structural information from NMR experiments is based on the dipolar coupling between protons. This interaction depends on the internuclear distances and the orientation of the internuclear vector relative to the static magnetic field. The distance and orientation dependence of dipolar couplings has long been used to characterize the structure of molecules by solid-state NMR spectroscopy.<sup>[2]</sup> However, in solution the dipolar couplings are averaged to zero as a result of the fast random reorientation of the molecule. Nevertheless, the randomly fluctuating magnetic field produced by one nucleus interacts with the spins of nearby nuclei and causes relaxation of their magnetization. This cross-relaxation effect is the basis of the NOE experiments and scales with the distance  $r$  between the nuclei ( $\propto r^{-6}$ ). In proteins, numerous proton–proton distances (with an upper limit of 5–6 Å) can be measured, which together define the three-dimensional structure. Difficulties arise if the number of experimental proton distances is sparse, as frequently found, for example, between different domains in a protein or in nucleic acids because of the small proton

density. As a consequence of the short-range nature of the NOE-derived distance restraints, it is also difficult to accurately define the relative orientation of regions which are far apart from each other in the three-dimensional structure of the molecule.

## Residual Dipolar Couplings

The shortcomings of NOE-based structure determination can be resolved by using novel structural information derived from residual dipolar couplings (RDCs). If a molecule is dissolved in a dilute liquid crystalline medium it becomes partially aligned. As a result, the dipolar couplings are not completely averaged to zero and lead to a small splitting of the NMR signals. Tjandra and Bax have shown that these RDCs provide unique long-range structural information since they define projection angles for internuclear bonds (for example, the peptide N–H bond) with respect to a molecule-fixed coordinate frame (Figure 1).<sup>[3]</sup> Since the degree of alignment can be tuned to be small, the molecule still reorients quickly in solution and the linewidths in the NMR spectra are almost unaffected. Thus, the structural information contained in RDCs can be retrieved without being

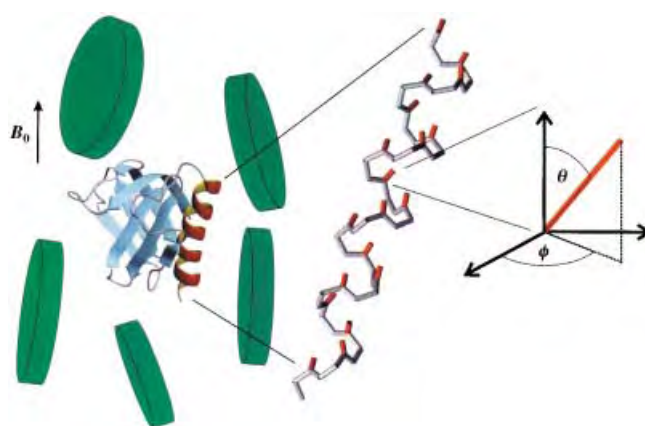


Figure 1. Partial alignment of a protein in a dilute liquid crystalline medium. Above a certain temperature disc-shaped bicelles (in green) align with respect to the static magnetic field  $B_0$ . A protein dissolved in such a dilute liquid crystalline medium becomes weakly aligned. This gives rise to residual dipolar couplings which depend on the angles ( $\theta$ ,  $\phi$ ) of the internuclear vector connecting the dipolar coupled spins (for example, the N–H bond) in the alignment frame.

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accompanied by the large linewidths associated with solid-state NMR spectra. The small degree of alignment (ca.  $10^{-3}$ ) is introduced by steric and/or electrostatic interactions of the molecule in a dilute liquid crystalline phase, but it can also result if a large anisotropic magnetic susceptibility of the molecule interacts with the static magnetic field. Nowadays, various alignment media are available, such as bicelles from lipid/detergent mixtures or filamentous phages, which allow the measurement of RDCs for virtually any molecule.<sup>[4]</sup>

The incomplete averaging of dipolar couplings in an anisotropic phase is described by an alignment tensor. This so-called “Saupe order matrix” is a symmetric and traceless second-rank tensor with five independent parameters. In the principal axis system of the alignment tensor, two parameters describing the axial ( $A_a$ ) and rhombic ( $A_r$ ) components of the alignment tensor and polar coordinates ( $r_{ij}$ ,  $\theta$ ,  $\phi$ ) describing the orientation of the internuclear vector connecting two dipolar coupled spins ( $i$ ,  $j$ ) suffice for calculation of the residual dipolar coupling constant  $D_{ij}$  (if we neglect internal dynamics) [Eq. (1)]:

$$D_{ij} = k_{ij}[A_a(3\cos^2\theta - 1) + \frac{3}{2}A_r\sin^2\theta\cos(2\phi)] \quad (1)$$

where  $k_{ij} = -\gamma_i\gamma_j\mu_0h/(16\pi^3r_{ij}^3)$ ,  $\gamma$  is the gyromagnetic ratio,  $r_{ij}$  is the distance between the dipolar coupled spins (assumed to be fixed).

#### Structural Restraints from RDCs

In order to retrieve the structural information, the projection angles of the internuclear vectors have to be derived from experimentally measured RDCs. If five or more RDCs are available for a given molecular fragment, the corresponding alignment tensor can be determined. Two different approaches have been proposed for utilizing the structural information contained in RDCs:

- 1) A pseudoenergy potential for the RDCs is implemented during the molecular dynamics/simulated annealing protocol of an NMR structure calculation.<sup>[5]</sup> The orientation of the alignment tensor is fitted during the calculation by minimizing the difference between experimentally determined and calculated RDCs. The magnitude of the alignment tensor ( $A_a$  and  $A_r$ ) can be derived beforehand from the distribution of measured RDCs,<sup>[6]</sup> and is either kept fixed or optimized<sup>[7]</sup> during the structure calculation. Recently it was shown that a priori knowledge of the alignment tensor is not required for directly refining a structure against measured RDC data.<sup>[8]</sup>

The deviation between experimentally measured and calculated RDCs defines a quality factor  $Q$ , which characterizes the agreement of the structure with the experimental RDCs, and is thus a measure of structural quality [Eq. (2)]:<sup>[9, 10]</sup>

$$Q = \sqrt{\frac{\sum (D_{ij}^{\text{exp.}} - D_{ij}^{\text{calcd}})^2}{\sum (D_{ij}^{\text{exp.}})^2}} \quad (2)$$

- 2) Alternatively, the alignment tensor and the individual bond projection angles can be determined simultaneously

by fitting the experimentally measured RDCs to a given structure or molecular fragment. In this case, the system of linear equations that relates the measured RDCs to the alignment tensor and the projection angles is solved by an efficient numerical technique called singular value decomposition.<sup>[11]</sup> A comparison of the alignment tensor obtained from this order matrix analysis for different domains of a protein provides information about their relative orientation and potential dynamics.

Both applications of RDC-derived orientational information have been shown to greatly improve the quality of NOE-based NMR structures, and in particular for characterizing the relative domain orientation and dynamics in biomacromolecules.<sup>[4, 5, 12]</sup>

The utility of RDCs has also been demonstrated in applications where only few NOE data are available, or where some structural information is already known.<sup>[4]</sup> Examples include the refinement of homology models, docking of two proteins of known structure, or fold determination by using molecular fragment replacement together with structure database searches. Together with the expected availability of the complete space of protein folds as determined from structural genomics, the three-dimensional fold of a protein can thus be rapidly determined from a known structural homologue. This RDC-based method may be considered as the NMR equivalent of molecular replacement techniques that are very useful for crystallographic structure determination.

#### De novo Structure Determination from RDCs

The approaches described above do not allow the three-dimensional structure of a protein to be determined from RDCs alone, that is, without additional structural information, such as from NOE data. This is a consequence of the degeneracy of RDCs with respect to the orientation of the internuclear vector. As can be seen from Equation (1), a given RDC value corresponds to an infinite number of combinations of angles  $\theta$  and  $\phi$ . The infinite set of solutions for the projection angles ( $\theta$ ,  $\phi$ ) for a given RDC can be reduced by: 1) measuring several RDCs between nuclei in a rigid molecular fragment, such as the peptide plane, and 2) by combining RDC measurements in at least two anisotropic media with different alignment tensors.<sup>[13, 14]</sup> The measurement of more than five RDCs within a planar or chiral molecular fragment allows its orientation to be defined with an eight or a fourfold degeneracy, respectively. Four possible orientations remain, even for a chiral fragment, since the signs of  $\theta$  or  $\phi$  in Equation (1) can be reversed independently without changing the RDC value. However, the ambiguities are further resolved if RDCs are measured for a second different alignment. In this case, a planar fragment, such as a peptide bond, is defined to its true orientation and the mirror image, and a chiral motif is uniquely determined.

Blackledge and co-workers have now succeeded in the de novo determination of the fold of a small protein from residual dipolar couplings alone (Figure 2).<sup>[1]</sup> In their approach, a least-squares-based search algorithm determines

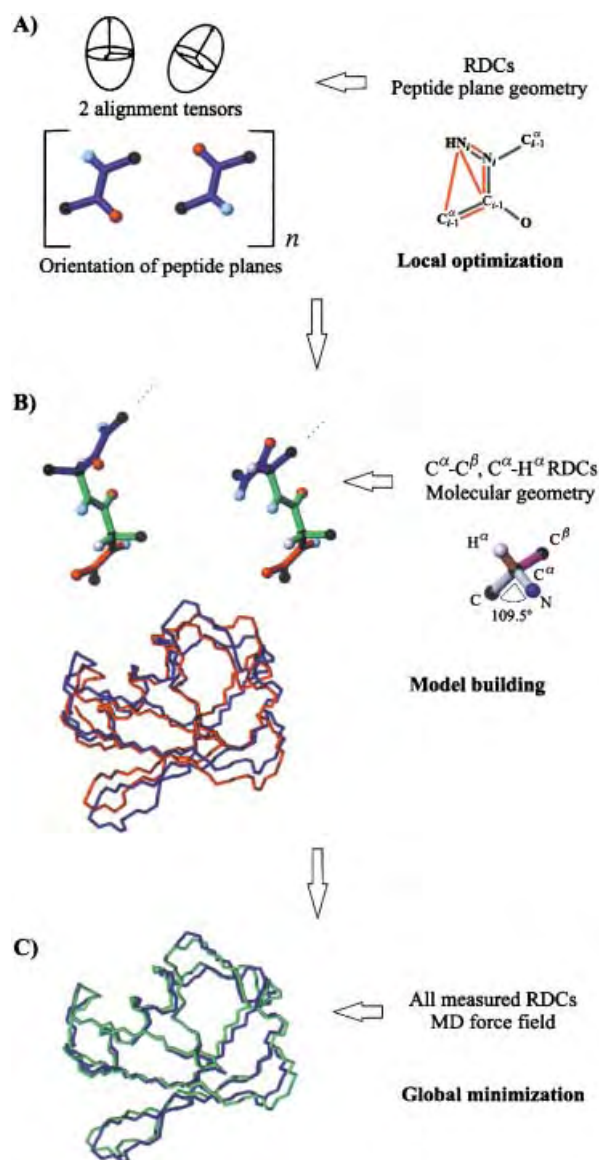


Figure 2. Flow chart for de novo determination of protein backbone structure from RDCs.<sup>[1]</sup> A) Two alignment tensors and the orientation of peptide planes in the protein are determined from RDCs (red lines) measured between nuclei in the peptide plane. This local optimization defines the orientations for the  $n$  peptide planes in the protein. However, the true and mirror image orientations cannot be distinguished at this stage. B) The information about the local orientation of each peptide plane is used to sequentially construct the peptide chain. RDCs involving the chiral  $C^\alpha$  atom are exploited to resolve the twofold degeneracy of the peptide plane orientations. Superposition of the resulting backbone structure (red) with the high-resolution NMR structure of ubiquitin (Protein Databank ID 1d3z,<sup>[10]</sup> blue) shows that the overall tertiary structure of the protein is defined, but with some local deviations. C) Finally, the structure is refined by a restrained molecular dynamics calculation which includes all measured RDCs. The resulting backbone structure of ubiquitin (green) is virtually identical to that determined from an extensive set of NOEs and RDCs (blue).

the orientation of the peptide plane from the RDCs measured between nuclei in the peptide plane in two different alignment media. The individual peptide planes are then sequentially connected and uniquely oriented based on RDCs measured at the chiral junction ( $C^\alpha$ ) of two neighboring peptide planes (Figure 2A). In most cases this uniquely defines the orienta-

tion of the peptide plane ( $i+1$ ) with respect to the peptide plane of the residue ( $i$ ). If some RDC data are missing, as for example in proline residues, the orientation is determined by including orientational information for neighboring residues and fitting the backbone angles in a multidimensional parameter optimization. Following this "tracing" of the peptide chain, the overall backbone conformation is directly refined against the measured RDCs in a molecular dynamics simulated annealing calculation as described above (Figure 2B). Blackledge and co-workers have applied this procedure to the protein ubiquitin, in which the most difficult case, a sequence of two proline residues for which limited orientational information was available, could be resolved successfully. The resulting RDC-based backbone structure of ubiquitin is virtually identical to a high-resolution NMR structure determined using a complete NOE data set (Figure 2C).

The achievement by Blackledge and co-workers represents a major breakthrough in the rapidly growing applications of residual dipolar couplings for structural studies by solution NMR methods. De novo determination of backbone structure from RDCs is fast and much more efficient than the standard NOE-based structure determination. Residual dipolar couplings are a first-order effect of the direct through-space interactions and are thus an order of magnitude larger than NOE effects, which result from second-order perturbation by dipolar couplings. Consequently, NMR experiments for measuring RDCs are rather sensitive, such that RDCs can be easily obtained between heteronuclear spins and at low sample concentration. Together with additional improvements in NMR methodology (TROSY),<sup>[15]</sup> labeling schemes, and hardware (cryogenic probes), which allow studies of high molecular weight systems by solution NMR spectroscopy, the use of orientational restraints derived from RDCs may in the future also allow the fold determination of larger proteins and their complexes.

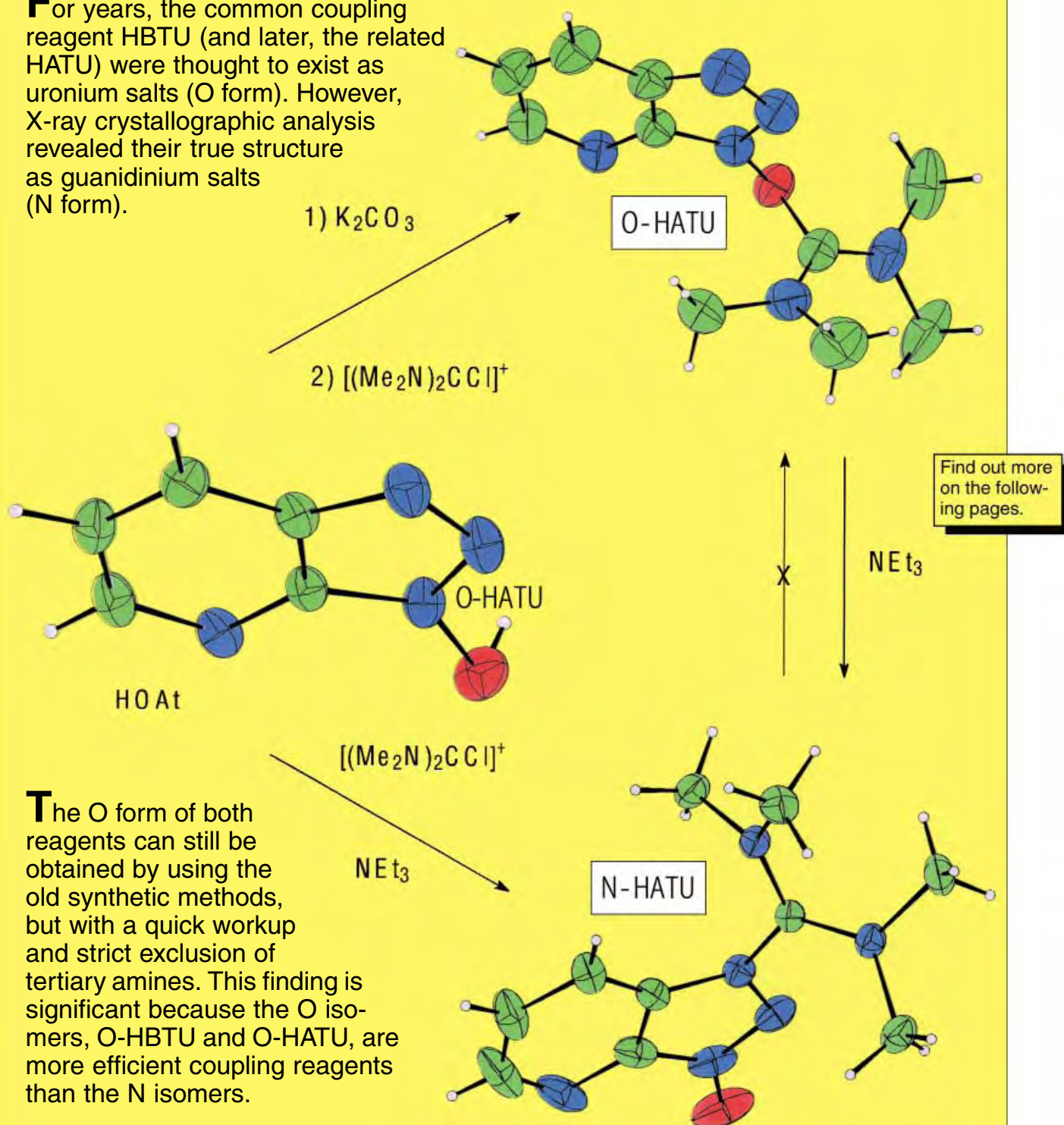
The discussion so far has neglected effects from internal dynamics on the measured RDCs. However, early studies have already suggested that RDCs may provide insight into internal dynamics of biomolecules, especially at time scales (milliseconds) that are difficult to assess by other NMR parameters.<sup>[16]</sup> The structural and dynamic description of a biomolecule by RDCs is complex, but initial studies are promising and indicate additional utility of RDCs for characterizing internal motions in proteins.<sup>[17, 18]</sup>

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**F**or years, the common coupling reagent HBTU (and later, the related HATU) were thought to exist as uronium salts (O form). However, X-ray crystallographic analysis revealed their true structure as guanidinium salts (N form).



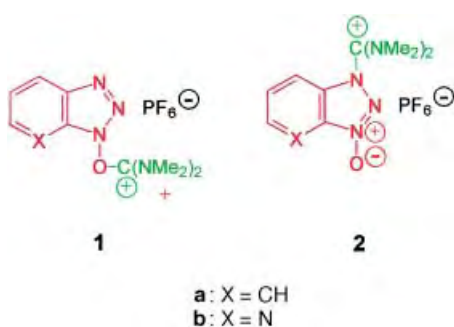
**T**he O form of both reagents can still be obtained by using the old synthetic methods, but with a quick workup and strict exclusion of tertiary amines. This finding is significant because the O isomers, O-HBTU and O-HATU, are more efficient coupling reagents than the N isomers.



# The Uronium/Guanidinium Peptide Coupling Reagents: Finally the True Uronium Salts\*\*

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Among the currently most popular peptide coupling reagents are the phosphonium<sup>[1,2]</sup> (BOP, PyBOP, etc.) and guanidinium<sup>[3]</sup> (HBTU, HATU, etc.) salts. When first described in 1978, HBTU was assigned the structure of uronium salt **1a**, presumably by analogy with the previously described phosphonium salts. In 1993, we synthesized HATU by using the same method,<sup>[4]</sup> and the analogous structure **1b** was assigned, in spite of the fact that <sup>1</sup>H NMR spectroscopic data



cited in both papers, viewed in the light of current knowledge,<sup>[5]</sup> might have suggested otherwise. A year later, X-ray crystallographic analysis and solution and solid-state NMR

spectroscopy showed that the true structures in both the crystalline state<sup>[6]</sup> and in solution<sup>[7,8]</sup> were the guanidinium isomers **2** and not the uronium isomers **1**. These results are in agreement with expected thermodynamic stabilities.<sup>[9]</sup>

By substituting KOBt<sup>[10]</sup> and KOAt<sup>[13]</sup> for HOBt and HOAt, and working up the reaction mixture quickly, we have now succeeded in preparing both these compounds in the originally postulated uronium form. These results are of special interest in view of the fact that the new uronium salts are more efficient coupling reagents than the corresponding guanidinium isomers. Although first examined in the case of a methyl-substituted HATU derivative<sup>[8]</sup> obtained from 4-Me-HOAt in which the methyl group interferes with the stability of the N-form, this structural element is not essential if attention is paid to the ease of isomerization of the O- to N-form by organic bases such as triethylamine. This process was easily followed in the IR spectrum (see below). The reverse rearrangement has never been observed. X-ray crystallography<sup>[14]</sup> was used to confirm that both HBTU and HATU obtained from the potassium salts are in the O-form (Figure 1).

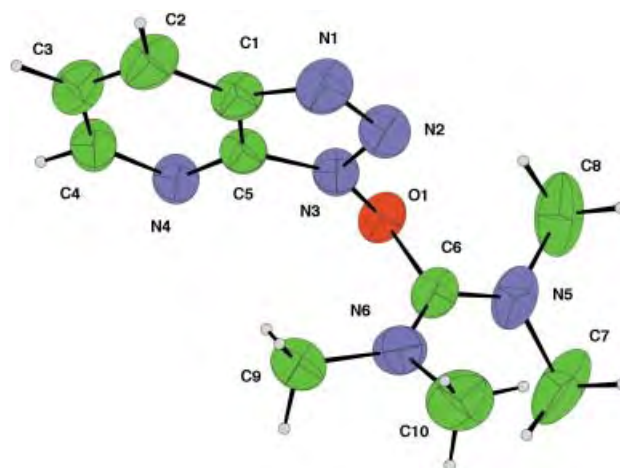


Figure 1. Crystal structure of **1b**.

Once several uronium compounds had been synthesized and their structures established by means of X-ray crystallographic analysis, we were able to find characteristic spectral absorptions that now easily allow structural assignment on the basis of IR, <sup>1</sup>H, and <sup>13</sup>C NMR analysis (Table 1). The IR spectra of salts derived from tetramethylurea showed characteristic absorptions at 1709–1711 for the O-isomers and at 1664–1675 cm<sup>−1</sup> for the N-derivatives. The twelve dimethylamino protons of the O-derivatives give rise to a singlet near δ = 3.24 in the <sup>1</sup>H NMR spectrum, whereas the N-compounds showed two singlets for six protons each near δ = 3.0 and 3.4. These differences in the proton NMR spectra agree with expectations based on the effect of hindered rotation in related systems.<sup>[5]</sup>

As expected (C–O vs C–N bond breaking),<sup>[15]</sup> amino acid activation through the authentic uronium salts proceeded more rapidly than through the isomeric guanidinium species under reaction conditions that avoided prior O → N rearrangement. Thus, Z-Aib-OH was converted into Z-Aib-OAt

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Table 1. IR,  $^1\text{H}$ , and  $^{13}\text{C}$ -NMR Absorptions for N- and O-HXTU Species<sup>[a]</sup>

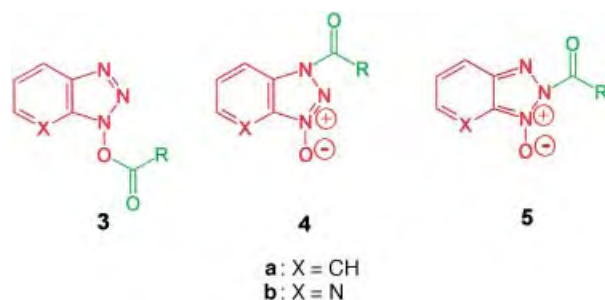
| Guanidinium Type |                         |                                  |                                     | Uronium Type |                         |                                  |                                     |
|------------------|-------------------------|----------------------------------|-------------------------------------|--------------|-------------------------|----------------------------------|-------------------------------------|
|                  | IR [ $\text{cm}^{-1}$ ] | $^1\text{H}$ -NMR <sup>[b]</sup> | $^{13}\text{C}$ -NMR <sup>[c]</sup> |              | IR [ $\text{cm}^{-1}$ ] | $^1\text{H}$ -NMR <sup>[b]</sup> | $^{13}\text{C}$ -NMR <sup>[c]</sup> |
| N-HATU           | 1668.9                  | 3.02s, 3.37s                     | 151.9                               | O-HATU       | 1711.5                  | 3.24s                            | 162.2                               |
| N-4-Me-HATU      | 1670.4                  | 3.02s, 3.48s                     | 150.1                               | O-4-Me-HATU  | 1711.5                  | 3.25s                            | 161.9                               |
| N-4-Cl-HBTU      | 1675.6                  | 3.00s, 3.44s                     | 149.3                               | O-4-Cl-HBTU  | 1711.1                  | 3.21s                            | 161.7                               |
| N-HBTU           | 1664.4                  | 3.02s, 3.37s                     | 152.7                               | O-HBTU       | 1709.3                  | 3.21s                            | 162.0                               |

[a] IR and NMR data were obtained in  $\text{CH}_3\text{CN}$  and  $\text{CD}_3\text{CN}$ , respectively. [b] Methyl protons. [c] Cationic carbon atom.

with O-HATU in the presence of one equivalent of collidine (half-life less than 2 min), whereas with N-HATU under the same conditions  $t_{1/2}$  was about 7 min. For HBTU,  $t_{1/2}$  was greater than 1 h for both O- (40% OBt ester at 1 h) and N-isomers (29% OBt ester at 1 h). As expected, these differences are reflected in the ease of peptide assembly, for example, in the assembly of the model decapeptide ACP by the so-called “ $1.5 \times 1.5$ ” system.<sup>[16]</sup> This represents a model in which a 1.5 molar excess of amino acid and a 1.5 min coupling time brings out the deficiencies of sub-optimal coupling reagents. For manual syntheses with N- and O-HATU, the crude peptide purity was 66.4 and 81.2%, respectively.

In the case of the activation and coupling of peptide segments, the coupling reagent determines the extent of epimerization as well as the yield. The best results were obtained in the presence of TMP base. Thus for the [2+1] coupling in DMF to form Z-Phe-Val-Pro-NH<sub>2</sub>,<sup>[17]</sup> a well-studied model, the extent of epimerization for O- and N-HATU and O- and N-HBTU in the presence of TMP/DIEA (1:1) was 3.4, 5.9, 10.3, and 20.6, respectively. In contrast, with DIEA, which rapidly effects isomerization, both O- and N-HATU lead to about 10% epimerization.

Our present recognition of the existence of stable O- and N-forms of the uronium/guanidinium type recalls the well-known establishment of the structure of the O- and N-acyl species **3** and **4**, respectively, which are generated during the activation of an acid in the presence of HOXt and a carbodiimide or through HXTU in the presence of a base.



These activated species have been considered to be the key participants in peptide coupling processes that occur in the presence of HOXt since the classical work of König and Geiger<sup>[18]</sup> on the value of HOBT as a coupling additive. Initially, in addition to the O-isomer **3a** and the N-isomer **4a**, a second N-acyl species **5a** was postulated. Although X-ray crystallography has been used to establish examples of **3** and **4** in different systems,<sup>[19]</sup> unequivocal evidence for structure **5** is lacking.

IR investigations into the activation process show that the O-form **3** is generated rapidly, and is subsequently isomerized to the N-form **4** more or less rapidly, depending on the nature of the system and/or solvent. Since the O-acyl form is more reactive,<sup>[20]</sup> such effects may be one factor in rationalizing the greater efficiency of carrying out peptide assembly with “low (short time) preactivation.” Examples include the Jung–Redemann decapeptide sequence<sup>[21]</sup> in the presence of N-HATU (51.4% yield with a 30-sec preactivation and 30.7% with a 7-min preactivation) and the formation of ACP<sup>[16]</sup> with N-TBTU (60.2% yield with a 30-sec preactivation and 34.1% with a 7-min preactivation (see Supporting Information).

A connection can be established between the two varieties of O-species discussed herein, since HPLC analysis allows the separation of the O- and N-acyl derivatives **3a** and **4a** for a number of simple amino acids such as Fmoc-Val-OH.<sup>[22]</sup> Thus treatment of Fmoc-Val-OH with O-HBTU in DMF in the presence of one equivalent of DIEA gave O-species **3** (99.5%) and N-acyl derivative **4** (0.5%) within 2 min (88:12 after 15 min). With N-HBTU the O-/N-isomer ratio after 2 min is 87.9:12.1, which suggests a clear relationship between the structure of the coupling reagent and that of the initial activation species. Since the major extent of acylation occurs in the first few minutes of reaction time, these effects, if shown to be general, can explain both the higher effectiveness of authentic uronium salts and short preactivation times.<sup>[23, 24]</sup>

A particularly clear indication of the enhanced reactivity of the O-series has been noted during a study of peptide cyclization (Table 2). On treatment with N-HBTU, more than 91% of the linear peptide is still unreacted after 15 s, whereas with O-HBTU over half has disappeared. A slightly greater yield of the *all*-L cyclic monomer is obtained with N-HBTU than with the O-isomer, and in contrast to segment condensation, the O-form results in almost twice the amount of epimerization. The reasons for the difference are not clear, although such effects have been observed in other cases between cyclization and ordinary segment condensation<sup>[25]</sup>

Table 2. Cyclization of H-Ala-Ala-BnAla-Ala-Ala-OH with O- and N-isomers of HBTU and HATU, %<sup>[a]</sup>

|                                             | O-HBTU                    | N-HBTU                   | O-HATU                   | N-HATU               |
|---------------------------------------------|---------------------------|--------------------------|--------------------------|----------------------|
| <i>all</i> -L-linear peptide <sup>[b]</sup> | 11.6(48.4) <sup>[c]</sup> | 9.0(91.2) <sup>[c]</sup> | 7.5(27.7) <sup>[c]</sup> | 0(45) <sup>[c]</sup> |
| <i>all</i> -L-cyclic monomer                | 31.4(18.4)                | 37.6(3.0)                | 56.3(46.5)               | 68.4(32.0)           |
| epimeric cyclic monomer                     | 7.5                       | 4.2                      | 4.1                      | < 4                  |

[a]  $10^{-3}\text{M}$  in DMF, coupling reagent (1.1 equiv), TMP (2 equiv), DIEA (1 equiv), HPLC analysis after 60 min. [b] epimerized linear precursor cannot be excluded. [c] values in parentheses are HPLC values after 15 sec.

and may reflect subtle variations in the extent of oxazolone formation, which could precede the two types of reaction.

Supporting Information Available: Experimental details for the synthesis of O-HBTU and O-HATU as well as appropriate IR and NMR spectra and the results of comparisons between the (a) O- and N-forms and (b) low and extended preactivation in model syntheses.

# Abbreviations

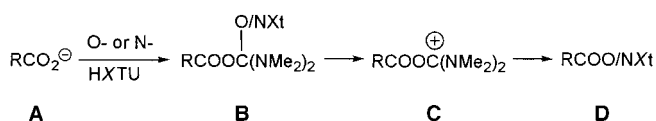
**Aib**:  $\alpha$ -aminoisobutyric acid, **ACP**: acyl carrier protein decapeptide, **BOP**: benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate, **DIEA**: *N,N*-diisopropylethylamine, **HAPyU**: 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridinylmethylene)pyrrolidinium hexafluorophosphate 3-oxide, **N-HATU**: 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium hexafluorophosphate 3-oxide, **O-HATU**: *N*-[(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate, **N-HBTU**: 1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium hexafluorophosphate 3-oxide, **O-HBTU**: *N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate, **HOAt**: 7-aza-1-hydroxybenzotriazole, **HOBt**: 1-hydroxybenzotriazole, **PyBOP**: benzotriazol-1-yl-*N*-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate, **TBTU**: tetrafluoroborate analogue of HBTU, **TMP**: 2,4,6-trimethylpyridine (collidine), **Z**: benzyloxycarbonyl.

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based on  $|F|$ , and by using anisotropic displacement parameters for P, O, F, C, and N atoms with fixed H atoms (CRYSTALS 2000: D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge, R. I. Cooper, Chemical Crystallography Laboratory, University of Oxford, Oxford, UK). Crystal structure data for **1b** ( $\text{C}_{10}\text{H}_{15}\text{OF}_6\text{N}_6\text{P}$ ) at 294 K: monoclinic, space group  $P2_1/n$ ,  $a = 6.3787(6)$ ,  $b = 19.696(5)$ ,  $c = 13.330(3) \text{ \AA}$ ,  $\beta = 99.94(1)^\circ$ ;  $V = 1649.6(6) \text{ \AA}^3$ ;  $Z = 4$ ;  $\rho_{\text{calc}} = 1.531 \text{ g cm}^{-3}$ ; crystal dimensions  $0.18 \times 0.18 \times 0.72 \text{ mm}$ ;  $R = 0.0630$ ;  $R_w = 0.0912$ , based on 1923 observed reflections ( $I > 1.96 \sigma(I)$ ); 3044 total;  $2\theta_{\text{max}} = 67^\circ$ ) and 218 refined parameters, including isotropic extinction correction. Decay and absorption corrections (transmission factors 0.64–0.67) were applied to the data; maximum residual electron density  $0.46 \text{ e \AA}^{-3}$ . Crystal structure data for **1a** ( $\text{C}_{11}\text{H}_{16}\text{OF}_6\text{N}_6\text{P}$ ) at 294 K: monoclinic, space group  $P2_1/c$ ,  $a = 8.3999(13)$ ,  $b = 28.799(4)$ ,  $c = 7.0528(5) \text{ \AA}$ ,  $\beta = 109.857(9)^\circ$ ;  $V = 1604.7(4) \text{ \AA}^3$ ;  $Z = 4$ ;  $\rho_{\text{calc}} = 1.570 \text{ g cm}^{-3}$ ; crystal dimensions  $0.29 \times 0.58 \times 0.58 \text{ mm}$ ;  $R = 0.0614$ ;  $R_w = 0.0786$ ; based on 2530 observed reflections ( $I > 1.96 \sigma(I)$ ); 3440 total;  $2\theta_{\text{max}} = 78^\circ$ ) and 272 refined parameters, including description of 50:50 disorder of the  $\text{PF}_6^-$  anion and isotropic extinction correction; maximum residual electron density  $0.32 \text{ e \AA}^{-3}$ . CCDC-163597 and CCDC-163598 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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- [24] The exact nature of the intermediates formed in a particular case depends on the substrate, solvent, identity and amount of base, and presence or absence of HOXt. For example, with N-TBTU in  $\text{CH}_2\text{Cl}_2$  in the presence of 2 equivalents of DIEA, Z-Gly-Ala-OH is converted into oxazolone in less than 2 min and OBt ester is formed only slowly ( $> 1 \text{ hr}$ ). If only 1 eq of DIEA is present or if 1 eq of HOBt is added, complete OBt ester formation occurs within 30 sec and the ratio does not change much thereafter. In the case of Fmoc-Aib-OH, N-HATU activation shows oxazolone ( $1690, 1829 \text{ cm}^{-1}$ ) along with O- ( $1819 \text{ cm}^{-1}$ ) and N-acyl ( $1722 \text{ cm}^{-1}$ ) species. After 5–6 min, oxazolone disappears, and some of the O-acyl derivative undergoes conversion into the N-acyl isomer so that the 3N form becomes the predominant species. Loss of configuration during segment coupling is thought to be related to the extent of oxazolone formation if a base is present. Other labile intermediates may precede formation of the OXt ester. A possible initial intermediate, following formation of the tetrahedral intermediate **B**, is the O-acyluronium cation **C**. For a



number of hindered acids (mesitoic, pivalic) authentic *O*-acyluronium salts have been isolated and identified. For the mesitoic acid derivative this species is more reactive than the OAt ester. Thus the exact timing of the possible formation of **C** and its conversion into active ester or its direct involvement in a reaction process may help to explain differences between N-HATU and N-HAPyU or between H-HATU and N-HBTU. The lifetime of intermediates such as **C** in the presence of good nucleophiles such as OXt<sup>(-)</sup> is believed to be low and their definite involvement in the activation process of any particular case has not yet been established. Intermediate **C** is most likely involved under conditions of no or low preactivation; these conditions are generally more favorable for both peptide assembly and low loss of configuration during segment coupling.

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## Capillary Electrophoresis Analysis of DNA Adducts as Biomarkers for Carcinogenesis\*\*

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Formation of DNA adducts through the formation of covalent DNA modifications by exogenous or endogenous reactive chemical agents appears to be one of the earliest events in the development of cancer. The formation of DNA adducts thus represents a detectable and critical step in carcinogenesis and thus may serve as an early biomarker.

To establish the pathological significance of DNA adducts in human diseases such as cancer, it is necessary to find high-sample-throughput methods for the simultaneous detection of the various classes of DNA adducts. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 470 000 people from nine European countries were interviewed about their dietary habits and lifestyles.<sup>[1]</sup> Blood samples were also taken for future analysis of biomarkers, such as DNA adducts.<sup>[2]</sup> In such studies the use of the ultrasensitive <sup>32</sup>P-postlabeling method<sup>[3]</sup> has a number of drawbacks: such as the lack of automation, the use of a strong  $\beta$  emitter, and the fact that the simultaneous detection of DNA adducts derived from different classes of carcinogens is not possible. Approximately 300  $\mu$ g of DNA or more are

necessary for the determination of DNA adducts by liquid chromatography coupled to mass spectrometry (LC-MS).<sup>[4]</sup> Although this method is very useful for characterizing unknown DNA adducts it cannot be used for routine analysis. The biggest problem is getting enough DNA for studies, because of the expensive hydrolysis of such large amounts of DNA, and the fact that only similar DNA adducts can be analyzed in a single analytical run. A new analytical method with a high-sample-throughput is therefore necessary to determine several classes of DNA adducts simultaneously in only 10  $\mu$ g of DNA. Fluorescence derivatization of nucleotides for the analysis of DNA adducts has been used by the research groups of Sharma and Giese since 1988<sup>[5]</sup> to replace the <sup>32</sup>P-postlabeling method. However, neither the described conjugation of ethylenediamine at the 5'-phosphate group of nucleotides<sup>[5a]</sup> followed by the derivatization with dansyl chloride or fluorescein isothiocyanate,<sup>[5b]</sup> nor fluorescence derivatization in one step with a histidine-binding group<sup>[5c, d]</sup> fulfills the requirements for high-sample-throughput analysis.

We present here a new method to determine DNA adducts. It involves the hydrolysis of DNA, fluorescence labeling of modified and unmodified nucleotides, micellar electrokinetic chromatography, and laser-induced-fluorescence detection (CE-LIF) with 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionylethylenediamine (BODIPY FL EDA) as the fluorescence marker. Selective conjugation of 2'-deoxynucleoside-3'-monophosphates (dNMPs) through the phosphate moiety to the amino linker of BODIPY FL EDA was conducted in the presence of the water-soluble carbodiimide 1-ethyl-3-(3'-*N,N'*-dimethylaminopropyl)-carbodiimide (EDC) to activate the phosphate moiety of the dNMPs.<sup>[6]</sup> However, this approach to derivatization excludes the use of fluorescence markers or buffer systems with carboxylic acid, primary amino, or phosphate groups. The only suitable buffer system for the derivatization was *N*-(2-hydroxyethyl)-piperazine-*N'*-2-ethane sulfonic acid (HEPES) at pH 6.5. The enzymatic hydrolysis of DNA was also carried out in HEPES buffer at pH 6.0 to avoid a purification step. Comparison with <sup>32</sup>P-postlabeling analysis showed that digestion of calf-thymus DNA (CT-DNA) in HEPES buffer resulted in the same amounts of dNMPs as with the routinely used procedure in sodium succinate.<sup>[7]</sup> The derivatization reaction was monitored by spectroscopic characterization (ESI-MS, <sup>1</sup>H, <sup>13</sup>C, <sup>11</sup>B, and <sup>19</sup>F NMR spectroscopy) of the conjugate formed between 2'-deoxyadenosine-3'-monophosphate and BODIPY FL EDA.

So far we have explored the application of this CE-LIF method to the detection of apurinic (AP) sites and to the determination of a number of endogenous and exogenous DNA adducts (Table 1) in various samples such as oligonucleotides, CT-DNA, or human DNA. The same conditions for derivatization and separation were used in all analyses. CE-LIF analysis of etheno-dAMP- (Figure 1 A) and 5-Me-dCMP-modified (Figure 1 B) oligonucleotides gave excellent separation of the dAMP and dCMP adducts from the four unmodified nucleotides. Etheno-DNA adducts are generated by the reaction of DNA bases with lipid peroxidation products derived from endogenous sources or from exposure to xenobiotics.<sup>[8]</sup> The exact quantitation of 5-Me-dCMP in

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 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

Table 1. The corrected migration time of modified and unmodified nucleotides

| Nucleotide                                                                        | Corr. MT (dAMP/nucleotide) |                  |
|-----------------------------------------------------------------------------------|----------------------------|------------------|
| 1, <i>N</i> <sup>2</sup> -propano-2'-deoxyguanosine-3'-monophosphate (Hex-dGMP)   | 0.78; 0.75                 | ( <i>n</i> = 2)  |
| 5-methyl-2'-deoxycytidine-3'-monophosphate (5-Me-dCMP)                            | 0.79 ± 0.01                | ( <i>n</i> = 32) |
| 2'-deoxycytidine-3'-monophosphate (dCMP)                                          | 0.81 ± 0.01                | ( <i>n</i> = 34) |
| 8-hydroxy-2'-deoxyguanosine-3'-monophosphate (8-HO-dGMP)                          | 0.83 ± 0.01                | ( <i>n</i> = 6)  |
| 2'-deoxythymidine-3'-monophosphate (dTMP)                                         | 0.938 ± 0.006              | ( <i>n</i> = 42) |
| 2'-deoxyguanosine-3'-monophosphate (dGMP)                                         | 0.962 ± 0.004              | ( <i>n</i> = 42) |
| 2'-deoxyadenosine-3'-monophosphate (dAMP)                                         | 1.000                      |                  |
| AP site                                                                           | 1.011 ± 0.002              | ( <i>n</i> = 6)  |
| adducts of benzo[ <i>a</i> ]pyrene diol epoxide (B[ <i>a</i> ]P-dGMP, 2nd isomer) | 1.17 ± 0.01                | ( <i>n</i> = 5)  |
| adducts of aristolochic acid I (dA-AAI, dA-AAII, dG-AAI)                          | 1.23; 1.19                 | ( <i>n</i> = 2)  |
|                                                                                   | 1.20; 1.17                 | ( <i>n</i> = 2)  |
|                                                                                   | 1.13; 1.11                 | ( <i>n</i> = 2)  |
|                                                                                   | 1.29 ± 0.01                | ( <i>n</i> = 5)  |
| adducts of benzo[ <i>a</i> ]pyrene diol epoxide (B[ <i>a</i> ]P-dGMP, 1st isomer) |                            |                  |
| 1, <i>N</i> <sup>6</sup> -etheno-2'-deoxyadenosine-3'-monophosphate (etheno-dAMP) | 1.38; 1.36                 | ( <i>n</i> = 2)  |

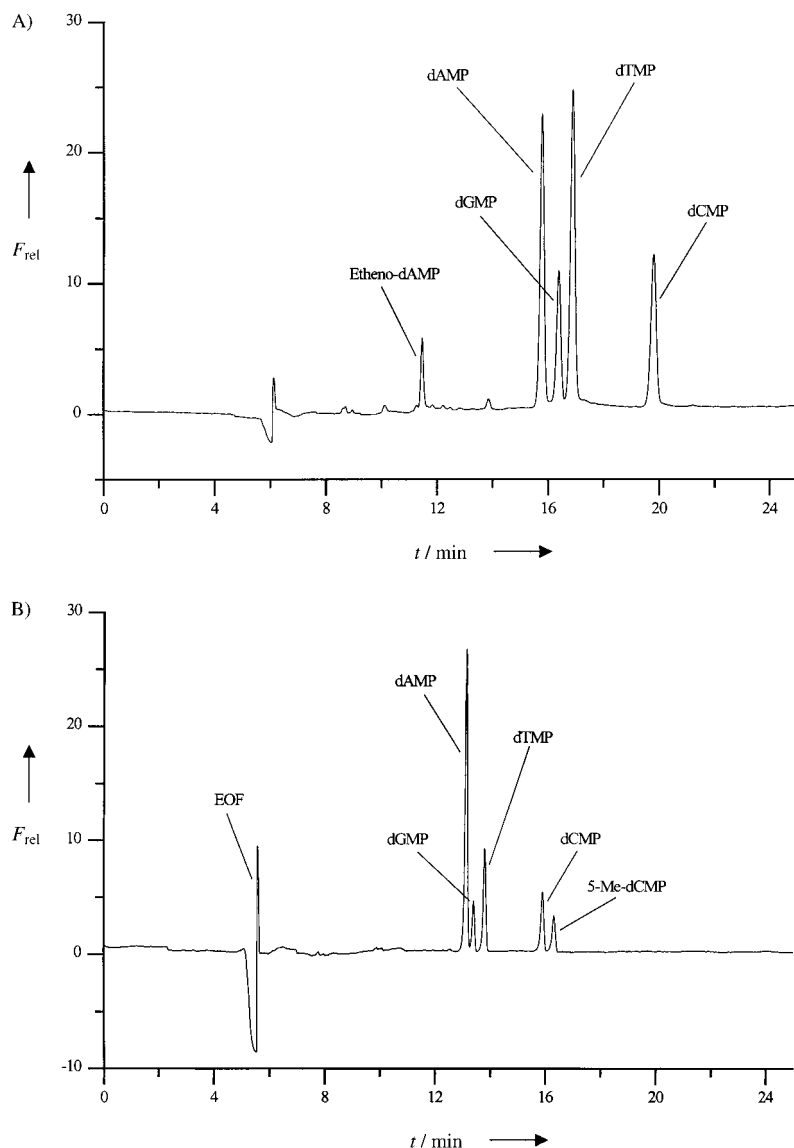


Figure 1. A) Analysis of etheno-dAMP: 10  $\mu$ g of a synthesized oligonucleotide with the sequence 5'-GAG.TCT.TCC.A\*GT.GTG.ATG.AT-3' (A\*: etheno-dAMP) were hydrolyzed, derivatized, and analyzed. Electrolyte: 75 mM sodium dodecyl sulfate (SDS) in 17 mM sodium phosphate buffer (pH 9.0) containing 15% (v/v) methanol; fused-silica capillary: total length: 50 cm; length to the detection window: 45.4 cm; inner diameter: 50  $\mu$ m; injection: 20 psi; temperature: 25  $^{\circ}$ C; applied voltage: 20 kV. The sample was diluted 10 000-fold with water. B) Analysis of 5-Me-dCMP: 10  $\mu$ g of a synthesized oligonucleotide with the sequence 5'-AGA.GC\*G.AGA.TTC.CAT.CA-3' (C\*: 5-Me-dCMP) were analyzed. The sample was diluted 10 000-fold with water. Separation conditions were as described in (A).

normal and tumor tissue will be an important application of this analytical method because hypomethylated DNA seems to play a key role in cancer.<sup>[9, 10]</sup> Figure 2 shows the analysis of an oligonucleotide modified with 8-HO-dGMP, a biomarker of oxidative stress.<sup>[11]</sup> The determination of 8-HO-dGMP is very difficult, because a time-dependent decomposition of 8-HO-dGMP to AP sites occurs. We believe that this is one reason for the imprecise data on 8-HO-dGMP, as discussed in the literature.<sup>[12]</sup>

Another sample investigated, CT-DNA, consisted of various adducts of aristolochic acid (AA-dNMP) which are established biomarkers for Chinese-herb nephropathy.<sup>[13]</sup> Figures 3 A and B show the analysis of CT-DNA and CT-DNA incubated with aristolochic acid I under zinc activation. A parallel <sup>32</sup>P-postlabeling analysis confirmed the presence of three DNA adducts specific for aristolochic acid (part of Figure 3b) as reported previously.<sup>[13]</sup> In contrast to <sup>32</sup>P-postlabeling analysis, the method introduced here allowed the simultaneous determination of unmodified nucleotides as well as the three adducts of aristolochic acid I: 5-Me-dCMP, AAI-dGMP, AAI-dAMP, and AAI-dAMP. A simultaneous determination of DNA adducts and 5-Me-dCMP is very interesting because of the suspected demethylation of CpG islands during cancerogenesis.

The reproducibility of the migration time (MT) is often poor in capillary electrophoresis because of the influence of the electroosmotic flow in uncoated fused-silica capillaries. To characterize DNA adducts in unknown samples we therefore standardized the MT of all unmodified and modified nucleotides to that of dAMP and obtained excellent reproducibility (standard deviation less than 3% by the use of different of capillaries and buffer charges). Table 1 lists the corrected MTs of all the analyzed nucleotides and the values are given as the mean and one standard deviation. A

difference of 0.02 in the corrected MT values between two nucleotides is necessary to ensure a baseline separation.

The reproducibility of the hydrolysis, derivatization, and separation was determined by analysis of aliquots of CT-DNA. The use of fluorescein as an internal standard made it possible to correct the peak areas and led to a relative standard deviation between 5.6 and 8.4% ( $n=29$ ) for the nucleotides.

The relative fluorescence quantum yield (QY) of each fluorescence-labeled nucleotide must be determined for an exact quantitation. The QY of the nucleotides were investigated and standardized to that of dAMP, which led to quantum factors of 1.00, 0.55, 0.97, and 0.98 for dAMP, dGMP, dTMP, and dCMP, respectively. The much lower quantum factor of dGMP arises from a quenching effect, which is dependent on the base.<sup>[14, 15]</sup> With the use of these factors the analysis of CT-DNA showed that  $6.43 \pm 0.13\%$  (RSD = 2.1%;  $n=6$ ) of all cytosine residues were methylated. Since no standard of 5-Me-dCMP was available, the QY of dCMP was used for both unmodified and modified cytosine.

The strength of the  $^{32}\text{P}$ -postlabeling procedure is the high sensitivity that is made possible by the enrichment of modified nucleotides by butanol extraction or digestion with nuclease P1. The strength of the CE-LIF method described here is its excellent selectivity. The samples must be diluted 100 fold because of the high salt concentra-

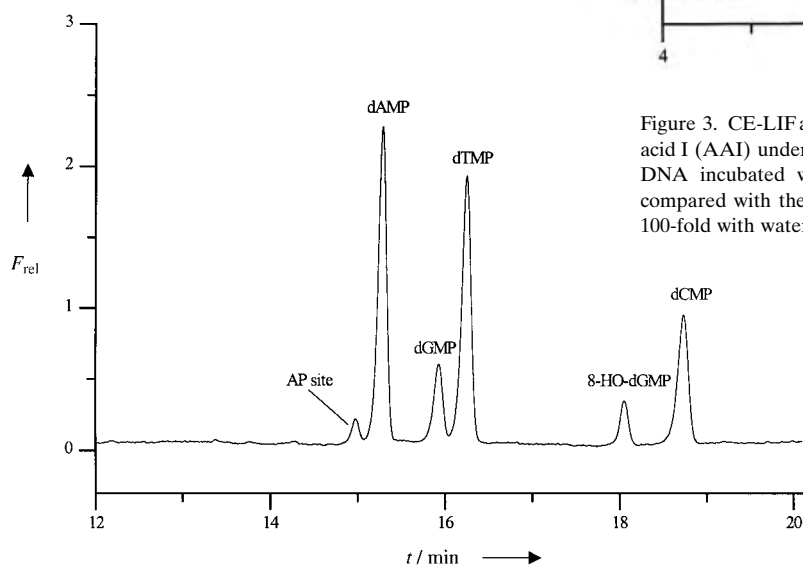


Figure 2. Analysis of 8-HO-dGMP and AP sites: 10  $\mu\text{g}$  of a synthesized oligonucleotide with the sequence 5'-GAG.TCT.TCC.AGT.G\*TG\*.ATG.AT-3' (G\*: 8-HO-dGMP) were analyzed. The sample was diluted 10000-fold with water. Separation conditions were as described in Figure 1.

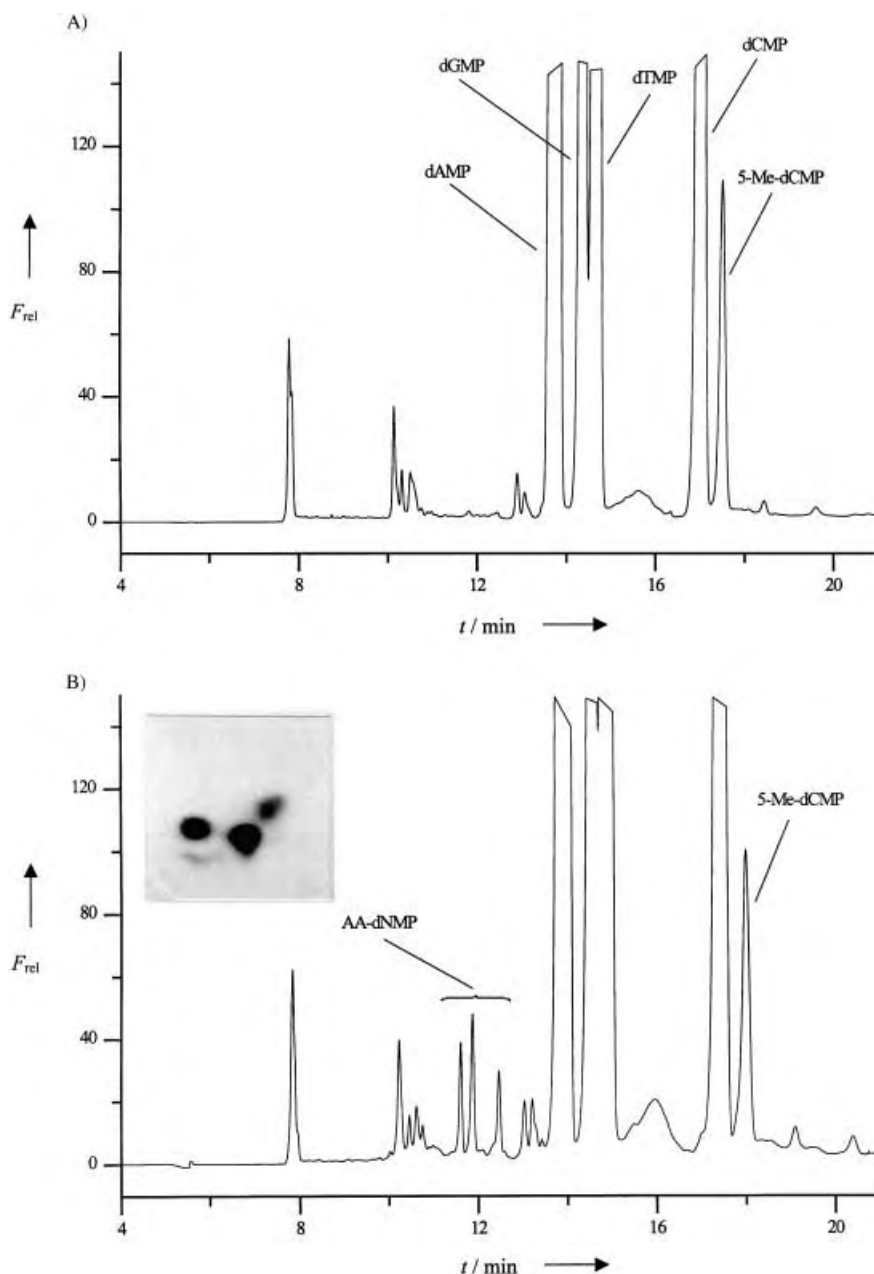


Figure 3. CE-LIF and  $^{32}\text{P}$ -postlabeling analysis of CT-DNA incubated with aristolochic acid I (AAI) under zinc activation: 10  $\mu\text{g}$  of normal CT-DNA (A) and 10  $\mu\text{g}$  of a CT-DNA incubated with AAI (B) were analyzed, and the electropherograms were compared with the results of the  $^{32}\text{P}$ -postlabeling method. The samples were diluted 100-fold with water. Separation conditions were as described in Figure 1.

tion and the great surplus of unmodified nucleotides. This procedure leads to a relatively high detection limit of 850 pM (determined for dAMP), which means in turn a relative adduct labeling (RAL) of 2 DNA adducts per  $10^6$  unmodified nucleotides (normals). The sensitivity could be improved to 50 pM or 1.4 DNA adducts per  $10^7$  unmodified nucleotides by using electrostacking with reversed field<sup>[16]</sup> as a focussing step.

The higher detection limit is nevertheless sensitive enough for the detection of many endogenous DNA adducts and the exact quantitation of DNA



methylation (5-Me-dCMP). We are continuing to improve the method by optimizing sample preparation to enrich modified nucleotides.

### Experimental Section

DNA hydrolysis: DNA (10 µg) was diluted in water (5.2 µL) and hydrolyzed by incubation for 3 h at 37 °C with an enzyme mixture (4.0 µL; micrococcal nuclease: 150 mU µL<sup>-1</sup> and spleen phosphodiesterase: 2.5 mU µL<sup>-1</sup>) and buffer (0.80 µL; 250 mM HEPES, 100 mM CaCl<sub>2</sub>, pH 6.0).

Fluorescence derivatization: 1.8 M EDC (30 µL; in 800 mM HEPES buffer, pH 6.5), 25 mM BODIPY FL EDA (30 µL; in 800 mM HEPES buffer, pH 6.5), and 800 mM HEPES buffer (20 µL) at pH 6.5, were added to the hydrolysate and incubated for 25 h at 25 °C in the dark.

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## Structure of Bis(pentafluorophenyl)xenon, Xe(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>\*\*

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*Dedicated to Professor Peter Sartori on the occasion of his 70th birthday*

Recently, we synthesized the first homoleptic organoxenon(II) compound with two Xe–C bonds, Xe(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub> (**1**), through the fluoride-initiated reaction of (CH<sub>3</sub>)<sub>3</sub>SiC<sub>6</sub>F<sub>5</sub> and XeF<sub>2</sub>.<sup>[1]</sup> An alternative route to **1** is the reaction of C<sub>6</sub>F<sub>5</sub>XeF and [Cd(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>].<sup>[2]</sup> Compound **1** is obtained as a white solid which explosively decomposes above –20 °C. However, as single crystals could not be grown, **1** was characterized exclusively in solution by <sup>129</sup>Xe, <sup>19</sup>F, and <sup>13</sup>C NMR spectroscopy.

The development of apparatus and methods has now advanced to the stage where it is possible to solve and refine even structures of complicated organic and organometallic compounds on the basis of X-ray powder data.<sup>[3]</sup> Since **1** is obtained as an almost single-phase microcrystalline powder, we were encouraged to determine the crystal structure from X-ray powder data despite of the extreme thermal instability of **1**.

Compound **1** was synthesized from (CH<sub>3</sub>)<sub>3</sub>SiC<sub>6</sub>F<sub>5</sub> and XeF<sub>2</sub><sup>[1]</sup> and investigated at –223 °C (see Experimental Section).<sup>[4]</sup> The powder diffractogram was indexed in a monoclinic unit cell,<sup>[5]</sup> and the volume of the unit cell was in good agreement with the calculated volume for four formula units. On the basis of the systematic absences, the only space group that came into consideration was *P*2<sub>1</sub>/*n*. Le Bail extraction<sup>[6–8]</sup> within this space group and a subsequent structure determination using direct methods<sup>[9]</sup> led to a position which was assigned to the Xe atom. As the positions of the C<sub>6</sub>F<sub>5</sub> rings could not be determined by using difference Fourier syntheses, we applied the method of “simulated annealing”.<sup>[10]</sup> Two “rigid bodies” were defined for the perfluorinated phenyl rings and placed on two arbitrary positions together with the position obtained for the Xe atom and used as starting parameters. After a few cycles, a reasonable structural solution was found which was refined by the Rietveld method.<sup>[11]</sup> On account of the limited quality of data as well as a large number of parameters, the C<sub>6</sub>F<sub>5</sub> rings were refined as rigid bodies (C–C 1.38, C–F 1.35 Å) and isotropic temperature factors of identical elements were constrained. A stable refinement resulted which quickly converged.<sup>[12]</sup>

The resulting molecular structure of **1** is shown in Figure 1. Both Xe–C distances (Xe–C11 2.394(9) Å, Xe–C21 2.35(1) Å) are almost identical within the double standard

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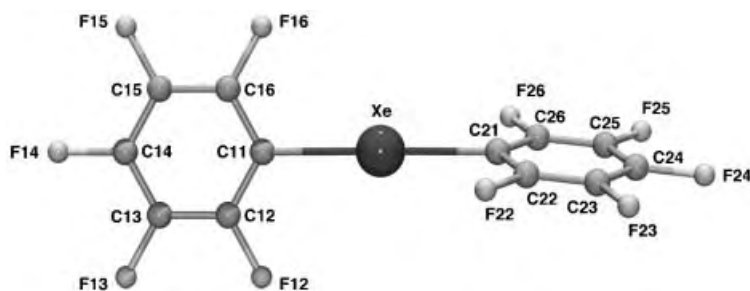


Figure 1. Molecular structure of **1** in the solid state; selected distances [Å] and angles [°]: Xe–C11 2.394(9), Xe–C21 2.35(1); C11–Xe–C21 178(3)°.

deviation. The Xe–C bonds are 0.3 Å longer than the corresponding bond in the  $\text{XeC}_6\text{F}_5^+$  ion in  $[\text{Xe}(\text{C}_6\text{F}_5)]\text{[AsF}_6\text{]}.$ <sup>[13]</sup> The C11–Xe–C21 unit is as expected almost linear (angle 178(3)°). The two  $\text{C}_6\text{F}_5$  rings are twisted by 72.5° with respect to each other. This torsion angle is comparable with that of the isoelectronic  $[\text{I}(\text{C}_6\text{F}_5)_2]^-$  ion (69.54°).<sup>[14]</sup>

Figure 2 depicts the molecular packing of **1**. Arrangement of molecules in layers parallel to the (100) plane is perceptible; symmetrically equivalent phenyl rings are arranged parallel to each other. Short distances are found pairwise between the rings (3.57 and 3.73 Å, cf. graphite: 3.40 Å)<sup>[15]</sup> which can be interpreted in terms of weak interactions. The next closest distances between the rings exceed 5.36 Å. Four intramolecular (3.30(1)–3.394(8) Å) and five intermolecular

(3.36(1)–3.536(9) Å) fluorine contacts are found in the coordination sphere of xenon being shorter than the sum of van der Waals radii of xenon and fluorine (3.63 Å).<sup>[16]</sup>

The experimental results are supported by electron-correlated ab initio calculations (MP2<sup>[17]</sup>) and density functional theory (DFT) calculations (B3LYP<sup>[18]</sup>), which were performed with quasi-relativistic pseudopotential basis sets (LANL2DZ,<sup>[19]</sup> CEP-121G,<sup>[20]</sup> SDD<sup>[21]</sup>) as well as the correlation-consistent cc-pVQZ basis set<sup>[22]</sup> for fluorine and carbon and the optimized Stuttgart–Dresden–Bonn<sup>[23]</sup> relativistic effective core potential (ECP46MWB<sup>[21]</sup>) for xenon (Table 1). Ge-

ometry optimizations and normal vibration analyses were carried out using Gaussian 98.<sup>[24]</sup> All calculated structures represent real minima of the potential hypersurface and do not give evidence for any imaginary frequencies.

Calculated bond lengths and angles of **1** at the DFT level are in better agreement with experimental results than those of prior calculations at the Hartree–Fock level.<sup>[2]</sup> Best results for Xe–C bond lengths were achieved with calculations at the B3LYP level using basis sets CEP-121G, LANL2DZ, and SDD. Also conformity of calculated and measured angles appears extraordinary.<sup>[25]</sup> Results at the MP2 level exhibit values that are too high, those at the HF level values that are too low. The well-known bad conformity of experimental values and HF calculations for non-metal fluorine derivatives

exhibits the necessity to take electron correlation into account to achieve sufficient agreements.<sup>[26, 27]</sup> The results using the combination HF/cc-pVQZ for geometry optimization correspond extensively with those of DFT calculations (B3LYP/SDD). The inclusion of polarized d, f, and g orbitals hardly influences the results at all.

The great deviation of the calculated dihedral angle C16–C11–C21–C26 from an angle of 90° may be attributed to intramolecular packing effects. To obtain further information on intramolecular interactions between Xe and F, the potential hypersurface was investigated as a function of the torsion angle by relaxed-potential energy-surface scans<sup>[28]</sup> using B3LYP/SDD calculations. The rotational barrier of the  $\text{C}_6\text{F}_5$  rings is about 1.2 kJ mol<sup>−1</sup>. The potential graph exhibits two saddle points at 40° and 60°. As a result, evidence for interactions of orbitals of the *ortho*-fluorine atoms and of the xenon atoms can be assumed.

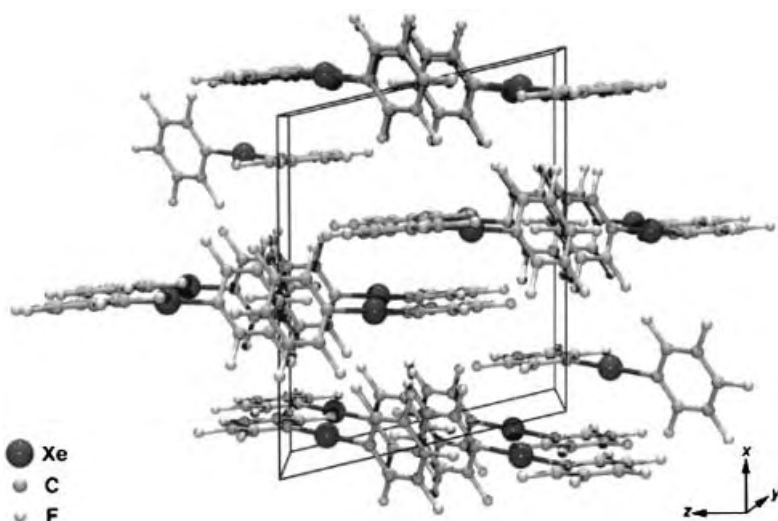


Figure 2. Molecular packing in the crystal structure of **1**.

Table 1. Experimental and calculated structural parameters [Å, °] and energies [kJ mol<sup>−1</sup>] of **1**.

|                           | Exp.                 | HF/LANL2DZ           | B3LYP/CEP-121G <sup>[a]</sup> | B3LYP/LANL2DZ | B3LYP/SDD | MP2/LANL2DZ | MP2/SDD |
|---------------------------|----------------------|----------------------|-------------------------------|---------------|-----------|-------------|---------|
| Xe–C11                    | 2.394                | 2.344 <sup>[2]</sup> | 2.394                         | 2.401         | 2.336     | 2.443       | 2.338   |
| Xe–C21                    | 2.35                 |                      |                               |               |           |             |         |
| Xe–F <sub>intramol.</sub> | 3.364 <sup>[b]</sup> | 3.369                | 3.427                         | 3.422         | 3.377     | 3.485       | 3.397   |
| C12–C11–C16               | 120                  | 117.4 <sup>[2]</sup> | 118.1                         | 118.5         | 118.1     | 117.8       | 118.2   |
| C11–Xe–C21                | 178                  | 180.0                | 180.0                         | 180.0         | 180.0     | 180.0       | 180.0   |
| C11–C12–F12               | 120                  | 119.4                | 119.7                         | 119.9         | 119.6     | 119.8       | 119.4   |
| <i>E</i>                  | –                    | 326.7                | 301.6                         | 306.0         | 305.7     | 298.9       | 297.5   |
| ZPE <sup>[c]</sup>        | –                    | 274.4                | 244.5                         | 249.7         | 249.5     | 241.7       | 240.9   |

[a] Consideration of 3df polarisation functions (CEP-121G(3df)) led to the following results: Xe–C11, Xe–C21 2.367, Xe–F<sub>intramol.</sub> 3.385, C12–C11–C16 118.8, C11–C12–F12 120.3, *E* = 325.2 kJ mol<sup>−1</sup>. [b] The mean was determined from the four shortest Xe–F contacts. [c] Zero-point energies.

# Experimental Section

**1:** Microcrystalline **1**<sup>[1]</sup> was slowly precipitated from CH<sub>2</sub>Cl<sub>2</sub>, purified, and dried in dynamic vacuum at –40 °C (10<sup>–3</sup> bar). Under an argon atmosphere, the residue was spread smoothly on a polymer foil at –100 °C using a spatula precooled to –196 °C. To prevent a loss of substance, the sample carrier was coated with perfluorinated silicon grease (Volltaeff). Samples prepared in this manner were additionally dried in vacuo at –40 °C and then transferred to the sample chamber of the X-ray powder diffractometer (Huber G645) at –100 °C, which was cooled to –223 °C for collecting diffraction data.

**Caution!** Pure Xe(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub> is thermally unstable and may vigorously explode on contact. Protection glasses and Kevlar gloves were worn throughout all manipulations.

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## As[P(NMe<sub>2</sub>)<sub>3</sub>]<sub>2</sub><sup>+</sup> as Simultaneous As<sup>I</sup> and P<sup>I</sup> Source: Synthesis and Density Function Calculations of Planar Tetracoordinate Arsonium and Phosphonium Ions\*\*

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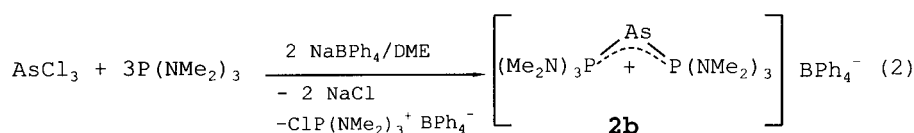
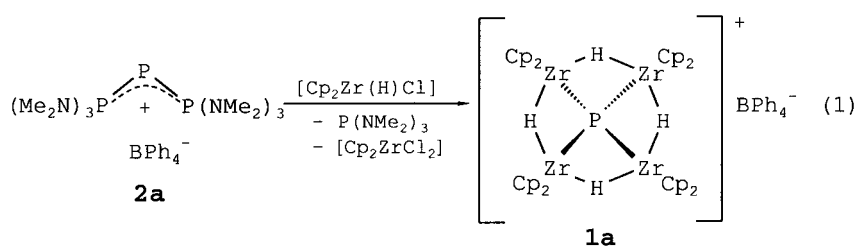
*Dedicated to Professor Rolf Gleiter on the occasion of his 65th birthday*

Recently we reported on the unusual organometallic phosphonium ion  $\text{P}[\text{Zr}(\text{H})\text{Cp}_2]_4^+$  ( $\text{Cp} = \eta\text{-C}_5\text{H}_5$ ) in the BPh<sub>4</sub>

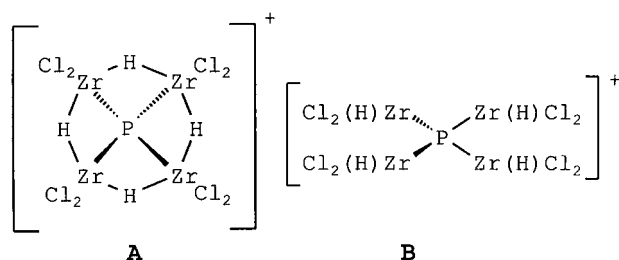
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salt **1a**, which surprisingly exhibited a planar tetracoordinate P atom and four Zr-bridging H atoms.<sup>[1]</sup> The cation is unprecedented amongst the previously known organometallic  $\text{PR}_4^+$  derivatives and forms the first phosphorus analogue of planar tetracoordinate methane derivatives.<sup>[2]</sup> Previously only tetragonal-pyramidal tetraaryls<sup>[3]</sup> and tetrahedral tetrastannyl-<sup>[4]</sup> and tetrasilylphosphonium ions<sup>[5]</sup> could be prepared. Compound **1a** is formed by the reaction of the triphosphonium salt  $[\text{P}(\text{NMe}_2)_3]_2^+\text{BPh}_4^-$  (**2a**) with the Schwartz reagent  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  in the presence of an auxiliary base; the diphosphane donor stabilized phosphonium ion functions as the  $\text{P}^{\text{I}}$  source and reacts by cleavage of the  $\text{P}(\text{NMe}_2)_3$  ligands and redox reactions to form the  $\text{PR}_4^+$  ion ( $\text{R} = \text{Zr}(\text{H})\text{Cp}_2$ ) [Eq. (1)].



According to ab initio calculations for the model cation  $[\text{P}(\text{Zr}(\text{H})\text{Cl}_2)_4]^+$  the anti-van't Hoff–Le Bel configuration **A**, unusual for a  $\text{PR}_4^+$  moiety with eight valence electrons, is 290 kJ mol<sup>-1</sup> more favorable than the tetrahedral configuration **B**. The preference for the planar configuration is attributed predominantly to the Zr–P  $\pi$  backbonds and delocalization of the lone pair electrons on the P atom in the HOMO as well as stabilization by the  $\mu_2$ -bridging H atoms at the Zr atoms by chelation.



In view of the existence of **1a** the question arises whether in analogy the homologous As salt  $[\text{As}(\text{Zr}(\text{H})\text{Cp}_2)_4]^+\text{BPh}_4^-$  (**1b**) exhibits a planar configured  $\text{AsR}_4^+$  ion, since ab initio calculations for the hypothetical ammonium ion  $[\text{N}(\text{Zr}(\text{H})\text{Cl}_2)_4]^+$  have shown that a highly distorted tetrahedral configuration would be preferred, not the planar or tetrahedral configurations.<sup>[1]</sup> In analogy to the synthesis of **1a**, the synthesis of **1b** should be possible by reaction of the diphosphane donor stabilized arsenium salt  $[\text{As}(\text{P}(\text{NMe}_2)_3)_2]^+$

$\text{BPh}_4^-$  (**2b**) with  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$ ; however, the precursor **2b** was hitherto unknown. In the following we therefore first describe the synthesis of **2b**, which surprisingly reacted with  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  not only to the planar arsonium ion in **1b**, but simultaneously also to the planar phosphonium ion in **1a**. In addition we report on the density functional theory (DFT) calculations for the homologous “real cations”  $[\text{E}(\text{Zr}(\text{H})\text{Cp}_2)_4]^+$  ( $\text{E} = \text{N}, \text{P}, \text{As}, \text{Sb}$ ) which confirm that the “magic” hydrido-zirconocenyl substituent is the ligand of choice to realize an anti-van't Hoff–Le Bel configuration in  $\text{ER}_4$  fragments with eight valence electrons.

As in the synthesis of **2a** described by Schmidpeter et al.,<sup>[6]</sup> the synthesis of **2b** is also simple. First the  $\text{As}^{\text{III}}$  ion in  $\text{AsCl}_3$  is reduced by  $\text{P}(\text{NMe}_2)_3$  in the presence of  $\text{NaBPh}_4$  to the  $\text{As}^{\text{I}}$  ion, which is donor-stabilized by the addition of two  $\text{P}(\text{NMe}_2)_3$  ligands [Eq. (2)]. Compound **2b** can be isolated in the form of colorless, highly air-sensitive crystals in 53 % yield.

Compound **2b** is stable only for a short time in polar, aprotic solvents such as THF, DME, or  $\text{CH}_2\text{Cl}_2$  at room temperature; after a few hours unknown orange-colored decomposition products are formed. The  $^31\text{P}\{^1\text{H}\}$  NMR spectrum of freshly prepared solutions at  $-30^\circ\text{C}$  also shows a singlet at  $\delta = 89.0$ , which indicates a degenerate, resonance-stabilized

P–As–P  $\pi$  system, a heteroallyl cation. In agreement with this a single-crystal X-ray structure analysis<sup>[7]</sup> of the THF solvate of **2b** shows only almost equal As–P distances of 2.266(2) and 2.236(2) Å (Figure 1). Very similar and almost identical As–P distances (2.24–2.27 Å) were also observed in the only

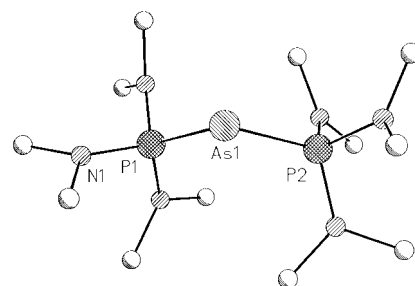
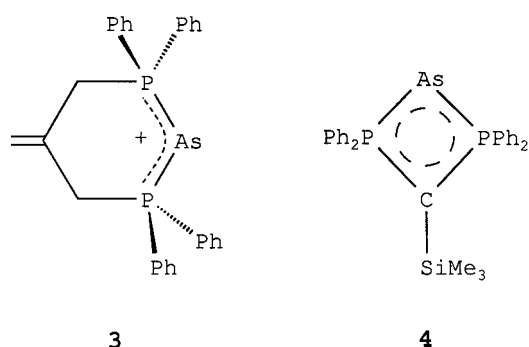


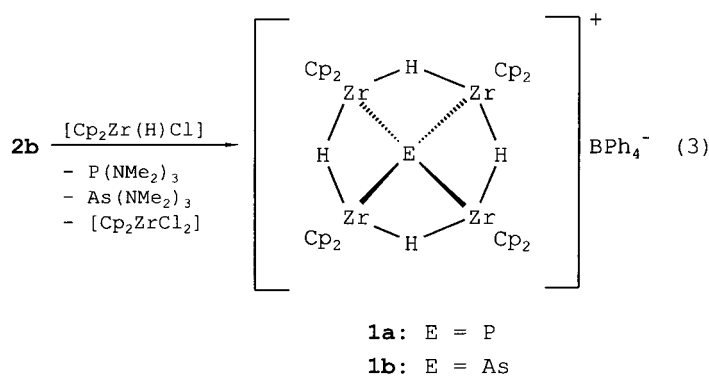
Figure 1. Molecular structure of **2b** in the crystal; selected distances [Å] and angles [°]: As1–P1 2.266(2), As1–P2 2.236(2), P1–N1 1.641(5); P1–As1–P2 103.26(6), As1–P1–N1 102.4(2).

previously known cyclic analogues **3**<sup>[8]</sup> and **4**<sup>[9]</sup> which equally exhibit P donor-stabilized  $\text{As}^{\text{I}}$  centers. The P1–As1–P2 angle in **2b** (103.26(6)°) is as expected larger than the corresponding endocyclic angles in **3** (93.0(1)°) and **4** (69.90(2)° and 69.45(2)°).

Compound **2b** reacts with a molar excess of  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  in THF to form a red suspension. Deep green crystals could be obtained from these solutions, which surprisingly turned out to be a mixture of the phosphonium and arsonium salts **1a** and



**1b**, respectively [Eq. (3)]. That both onium ions really exist in the mixtures followed from the electrospray ionization (ESI) mass spectra, in which the signals for the molecular ions occur at  $m/z$  920.4 (**1a**; calcd 920.6) and 964.1 (**1b**; calcd 964.5) as base peaks.



The composition of the mixtures was established unequivocally by the simple and readily distinguishable  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectra. The signals of the highly deshielded  $^1\text{H}$  nuclei of the bridging hydrogen atoms, which form different splitting patterns in the high-field region, are particularly characteristic. The doublet at  $\delta = -3.85$  ( $^2J(\text{H},\text{P}) = 29.5$  Hz) could be unambiguously assigned to **1a**, the singlet at  $\delta = -3.99$  to **1b**. The  $^{31}\text{P}$  NMR spectrum of  $[\text{D}_8]\text{THF}$  solutions shows a quintet for **1a** at  $\delta = 252.0$  ( $^2J(\text{P},\text{H}) = 29.5$  Hz).<sup>[1]</sup> By fractional crystallization from  $\text{CH}_2\text{Cl}_2/\text{pentane}$  the **1a/1b** ratio could be enriched from an initial 1:1 to a maximum of about 2:3 in favor of **1b**. Why formation of both onium ions occurs simultaneously, however, is still unknown. However, it is clear that "free" **2b** in solution does not rearrange to "free" **2a**. The As/P interchange necessary for the formation of **1a** must therefore presumably take place within the coordination sphere of the Zr atoms.

By single-crystal X-ray structure analysis<sup>[7]</sup> of the **1a/1b** mixed crystal (monoclinic space group  $C2/c$  as in pure **1a**)<sup>[1]</sup> in the ratio of 2:3, it was possible to show that in agreement with the  $^1\text{H}$  NMR spectroscopic results the two onium ions are indeed isostructural and exhibit a planar tetracoordinate phosphorus and arsenic atom, respectively (Figure 2). Naturally, mean Zr–E distances (E = P, As) are obtained which as expected are larger than the distances in pure **1a**.

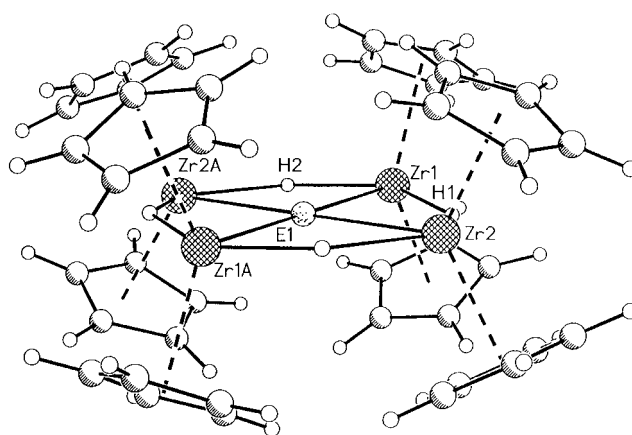


Figure 2. Molecular structure of the isostructural cations in **1a** (E = P) and **1b** (E = As) in the mixed crystal (ratio ca. 2:3); selected distances [Å] and angles [°]: E1–Zr1 2.6563(7), E1–Zr2 2.6470(8), Zr1–H1 1.97(6), Zr1–H2 1.99(7), Zr2–H2 2.03(7), Zr2–H1 2.10(7); Zr1–E1–Zr2 89.82(2), Zr1A–E1–Zr2 90.18(2), E1–Zr1–H1 68(2), E1–Zr1–H2 66(2), H1–Zr1–H2 135(2), Zr1–H1–Zr2 134(2); sum of angles at E1 360.0.

The preference for the planar configuration of the P and As onium ions was confirmed by DFT calculations (Figure 3, Table 1).<sup>[10]</sup> These showed that the planar configurations are

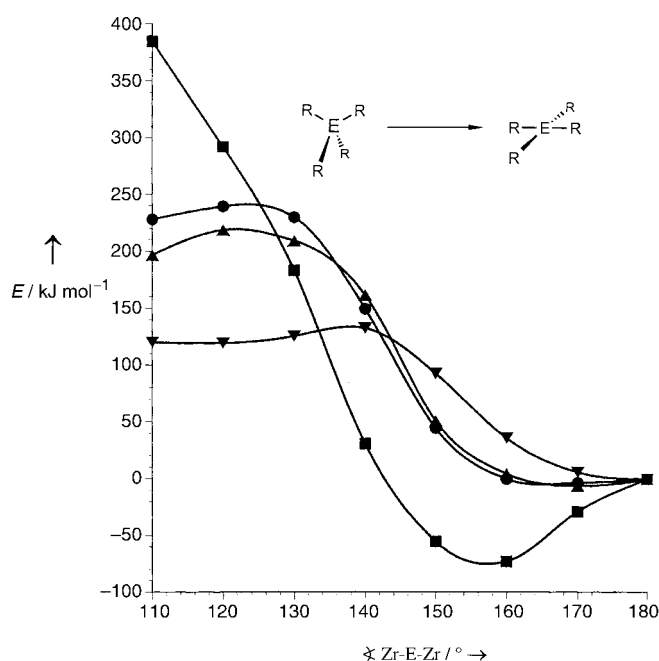


Figure 3. DFT-calculated energy profiles (relative to the energy of the planar form) as a function of the *trans*-Zr–E–Zr angle for the angle distortion of the  $\text{ER}_4^+$  ions (E = N, P, As, Sb; R = Zr(H)Cp<sub>2</sub>) from tetrahedral to planar.<sup>[10]</sup> ■ = N, ● = P, ▲ = As, ▼ = Sb.

Table 1. DFT-calculated geometric parameters for  $\text{E}[\text{Zr}(\text{H})\text{Cp}_2]_4^+$ .<sup>[10]</sup>

| E  | $\angle \text{Zr-E-Zr}$ [°] | $R_{\text{E-Zr}}$ [Å] | $R_{\text{Zr-H}}$ [Å] | $\angle \text{Zr-H-Zr}$ [°] |
|----|-----------------------------|-----------------------|-----------------------|-----------------------------|
| N  | 158.0, 92.0                 | 2.352                 | 1.945                 | 120.9                       |
| P  | 173.4, 90.2 <sup>[a]</sup>  | 2.647 <sup>[b]</sup>  | 2.043 <sup>[c]</sup>  | 133.3                       |
| As | 173.9, 90.2                 | 2.699                 | 2.065                 | 135.6                       |
| Sb | 175.4, 90.0                 | 2.830                 | 2.133                 | 139.7                       |

Experimental values: [a] 89.84(4), 90.16(4)°. [b] 2.616(1), 2.610(2) Å. [c] 1.93, 2.07, 2.12 Å.

240 (**1a**) and 195 kJ mol<sup>-1</sup> (**1b**) more favorable than the tetrahedral configurations. Also for the hypothetical stibonium homologue Sb[Zr(H)Cp<sub>2</sub>]<sub>4</sub><sup>+</sup> the planar form is favored by about 120 kJ mol<sup>-1</sup>. In contrast, however, the calculations for the ammonium homologue N[Zr(H)Cp<sub>2</sub>]<sub>4</sub><sup>+</sup> gave a highly distorted tetrahedral coordination geometry at the N atom with Zr–N–Zr angles of 158.0 and 92.0°, which should be 390 kJ and 75 kJ mol<sup>-1</sup> more favorable than the tetrahedral (109.47°) and planar forms (180°), respectively. The energy profiles show that the energy hypersurfaces of the P, As, and Sb onium ions in the region of the minimum structure are not only noticeably flat, but also very similar in appearance. The somewhat different curve shape for the Sb[Zr(H)Cp<sub>2</sub>]<sub>4</sub><sup>+</sup> ion in the region of Zr–Sb–Zr angles < 140° indicates the formation of terminal Zr–H and readily flexible Sb–Zr bonds. In contrast the Zr–N–Zr angles in the ammonium ion are far less flexible, which is attributable to stronger Zr–N bonds arising from isovalent s,p hybridization.<sup>[11]</sup> The synthesis of the ammonium homologue of **1a** and **1b** appears especially attractive because in that way a novel “intermediate” structural type for ER<sub>4</sub> compounds with eight valence electrons in an anti-van’t Hoff–Le Bel configuration would be realized.

### Experimental Section

All work was carried out under the strict exclusion of air and water. The solvents used were freshly distilled, dried, and saturated with Ar.

**2b**: AsCl<sub>3</sub> (1.52 g, 8.4 mmol) was added dropwise at –30 °C to a solution of NaBPh<sub>4</sub> (6.0 g, 17.4 mmol) and P(NMe<sub>2</sub>)<sub>3</sub> (4.74 mL, 26.1 mmol) in DME (130 mL). The yellow suspension was warmed to room temperature over 2 h and stirred for a further 2 h. The solid isolated by filtration was taken up in CH<sub>2</sub>Cl<sub>2</sub> (100 mL); the suspension was stirred for 15 min and then filtered. After concentration of the clear filtrate to about 10 mL colorless crystals of **2b** were obtained at 6 °C. Yield: 3.20 g (4.45 mmol, 53 %). M.p. 187–189 °C (decomp); <sup>1</sup>H NMR (250 MHz, [D<sub>8</sub>]THF): δ = 2.64 (m, 36H; N–CH<sub>3</sub>), 6.81 (m, 4H; arom. H), 6.93 (m, 8H; arom. H), 7.33 (m, 8H; arom. H); <sup>31</sup>P{<sup>1</sup>H} NMR (101.3 MHz, [D<sub>8</sub>]THF): δ = 89.0 (s); correct C,H analysis.

**1a/1b**: A slurry of [Cp<sub>2</sub>Zr(H)Cl] (2.56 g, 9.93 mol) in THF (10 mL) was treated with a solution of **2b** (0.86 g, 1.08 mmol) in THF (20 mL). The red suspension obtained was stirred for four days and then centrifuged. The clear filtrate was evaporated to dryness in vacuum and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (ca. 30 mL). Vapor diffusion of pentane (ca. 30 mL) into this solution gave deep green crystals within seven days at room temperature which were washed with cold CH<sub>2</sub>Cl<sub>2</sub> and then dried. Yield: 0.24 g (1:1 mixture of **1a** and **1b**, 24 %). <sup>1</sup>H NMR (250 MHz, [D<sub>8</sub>]THF): δ = –3.99 (s, AsZr–H of **1b**), –3.85 (d, <sup>2</sup>J(P,H) = 29.5 Hz, PZr–H of **1a**), 6.00 (s, C<sub>3</sub>H<sub>5</sub>), 6.80 (m, arom. H), 7.00 (m, arom. H), 7.43 (m, arom. H); <sup>31</sup>P NMR (101.3 MHz, [D<sub>8</sub>]THF): δ = 252.0 (q, <sup>2</sup>J(P,H) = 29.5 Hz, **1a**); ESI-MS (CH<sub>2</sub>Cl<sub>2</sub>/CHCl<sub>3</sub>): m/z (%): 920.4 [**1a** – BPh<sub>4</sub><sup>–</sup>] (100), 964.1 [**1b** – BPh<sub>4</sub><sup>–</sup>] (100).

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# Gold–Xenon Complexes\*\*

Thomas Drews, Stefan Seidel, and Konrad Seppelt\*

The recent isolation of the metal–xenon compound  $[\text{AuXe}_4]^{2+}(\text{Sb}_2\text{F}_{11})^-$  (**1**)<sup>[1]</sup> raises a number of questions. The salt **1** is formed from  $\text{Au}^{2+}$ , dissolved in  $\text{HF}/\text{SbF}_5$ , in the presence of xenon. If the concentration of  $\text{SbF}_5$  is fairly high (ca. 0.5 mol  $\text{SbF}_5$  in 1 mol  $\text{HF}$ ) **1** forms as the sole product in two crystallographically different modifications: a triclinic modification,<sup>[1]</sup> and a tetragonal modification, which has been seldomly observed. Both modifications differ only with respect to the cation–anion interactions. The triclinic modification has one particularly short  $\text{Au}\cdots\text{F}$  contact ( $\text{Au}\cdots\text{F12}$  267.1(4) pm; Figure 1 a), which supplements the square  $[\text{AuXe}_4]^{2+}$  unit resulting in a square pyramid. In the tetragonal modification the contacts are weaker ( $\text{Au}\cdots\text{F10}$  292.8(7) pm; see Figure 1 b). The ESR spectra of such reaction mixtures are quite complex and dependent on the xenon pressure and on the temperature—this is a first indication that in solution mixtures of products are present.

The first question is then whether only  $[\text{AuXe}_4]^{2+}$  exists, or if, during the ligand substitution on  $\text{Au}^{2+}$  with xenon, intermediates of the kind  $[\text{AuXe}_n]^{2+}$  ( $n < 4$ ) can also be isolated. Of the many parameters that can be varied in these experiments the xenon pressure and the acid strength of the  $\text{HF}/\text{SbF}_5$  play a dominant role. The importance of the Xe pressure is clear, that of the acid strength of the  $\text{HF}/\text{SbF}_5$  arises since upon reduced acidity  $\text{HF}^-$  or  $[\text{SbF}_6]^-$  could replace xenon as a ligand. We succeeded in isolating *cis*- $[\text{AuXe}_2]^{2+}(\text{Sb}_2\text{F}_{11})^-$  (**2**) in the form of violet-black crystals from solutions of  $\text{HF}/\text{SbF}_5 \approx 2:1$  after removal of excess xenon under vacuum at  $-78^\circ\text{C}$ . The crystals of **2**, like those of **1**, are strongly dichroic. The crystal structure of **2** is shown in Figure 2. The gold atom resides in a square-planar environment, surrounded by the two Xe atoms and two F atoms of the  $[\text{Sb}_2\text{F}_{11}]^-$  ion. The Au–Xe distances of 265.8(1) and 267.1(1) pm are slightly shorter than those in the  $[\text{AuXe}_4]^{2+}$  ion. Also the  $\text{Au}\cdots\text{F}$  contacts are quite short: 218.1(4) and 223.8(4) pm. Salt **2** is thermally slightly more stable than **1** with respect to loss of Xe.

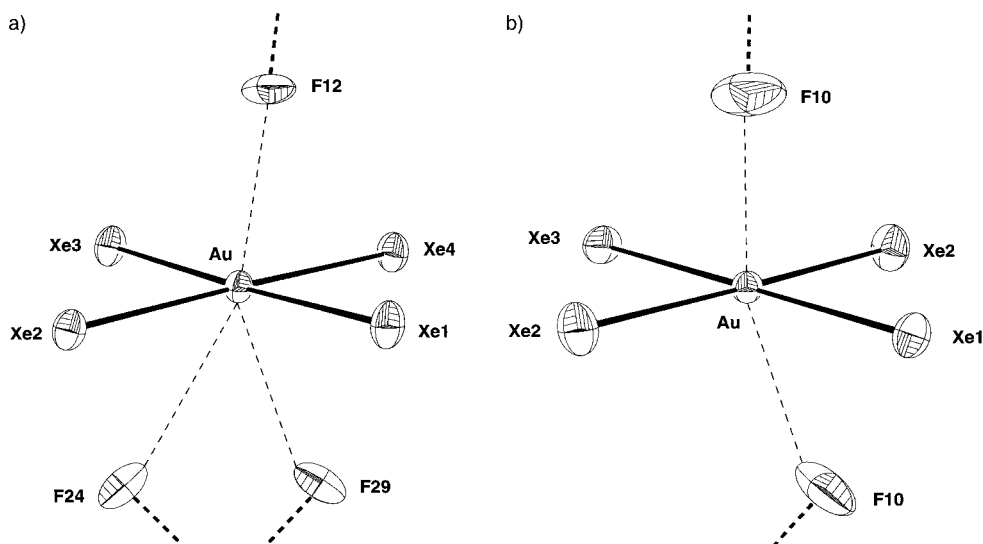


Figure 1. The  $[\text{AuXe}_4]^{2+}$  ion and its closer fluoride environment in the two crystallographically different modifications (ORTEP representation with 50% probability ellipsoids). a) Triclinic modification; bond lengths [pm]: Au–Xe1 273.30(6), Au–Xe2 274.98(5), Au–Xe3 277.79(6), Au–Xe4 274.56(5), Au–F12 267.1(4), Au–F24 315.3(4), Au–F29 295.0(4). b) Tetragonal modification; bond lengths [pm]: Au–Xe1 273.7(1), Au–Xe2 275.9(1), Au–Xe3 267.0(1), Au–F10 292.8(7).

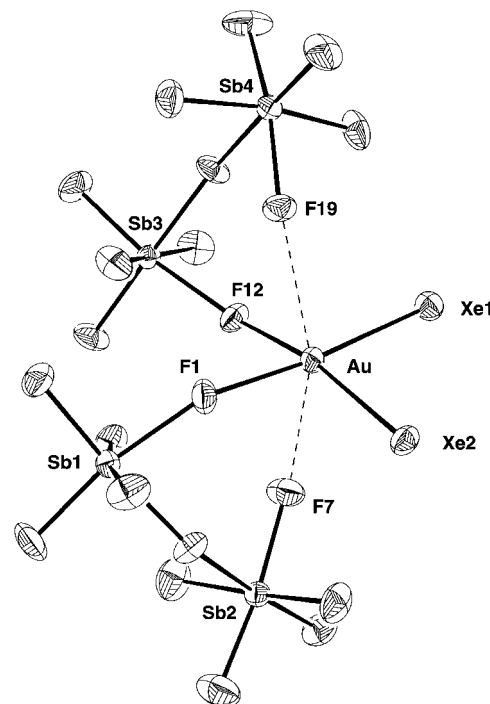


Figure 2. Structure of **2** (ORTEP representation with 50% probability ellipsoids); selected bond lengths [pm]: Au–Xe1 265.8(1), Au–Xe2 267.1(1), Au–F1 218.1(4), Au–F12 223.8(4).

We have also isolated the *trans*- $[\text{AuXe}_2]^{2+}$  ion but in this case as the  $[\text{SbF}_6]^-$  salt, *trans*- $[\text{AuXe}_2]^{2+}(\text{SbF}_6)^-$  (**3**). Unlike **1** and **2**, however, **3** was not prepared by reaction of  $\text{AuF}_3$  and Xe in  $\text{HF}/\text{SbF}_5$ , but rather by oxidation of finely divided gold in  $\text{HF}/\text{SbF}_5$  with  $\text{XeF}_2$  under pressure of xenon. Salt **3** forms ochre-colored, thermally very unstable crystals; the crystal structure is depicted in Figure 3. The Au–Xe distance of 270.9(1) pm is slightly longer than that in the *cis* compound **2**.

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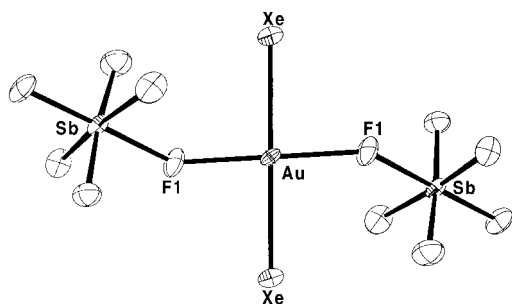


Figure 3. Structure of **3** (ORTEP representation with 50% probability ellipsoids); selected bond lengths [pm]: Au–Xe 270.9(1), Au–F1 215.9(6), Sb–F1 198.6(6).

The Au atom in **3** resides in a square-planar environment, with the Au atom coordinated to two Xe atoms and to two fluorine atoms of the  $[\text{SbF}_6]^-$  ions. The Au...F distances of 215.9(6) pm are markedly shorter than in the *cis* isomer **2**, due to the higher basicity of  $[\text{SbF}_6]^-$  in comparison to  $[\text{Sb}_2\text{F}_{11}]^-$ . That **3** is thermally less stable than **2** is possibly attributed to the anion:  $[\text{Sb}_2\text{F}_{11}]^-$  salts of weak bases are generally more stable than the corresponding  $[\text{SbF}_6]^-$  salts. The intense Raman band at  $121\text{ cm}^{-1}$  is assigned to the symmetric  $\text{AuXe}_2$  stretch. Obviously xenon has a larger *trans* effect for  $\text{F}^-$  since replacement of two xenon ligands in  $\text{AuXe}_4^{2+}$  should result in *cis*- $\text{AuXe}_2^{2+}$ , while introduction of two xenon ligands into  $\text{Au}^{2+} \cdot (\text{HF})_x$  should give the *trans*-product.

If in the syntheses a lower Xe pressure is applied, green crystals are isolated, which are remarkably stable and decompose only slightly below room temperature if moisture is excluded. The single-crystal structure determination reveals a binuclear Au–Xe complex containing a Z-shaped  $[\text{Xe-Au-F-Au-Xe}]^{3+}$  ion (Figure 4). Again the Au atom resides in a

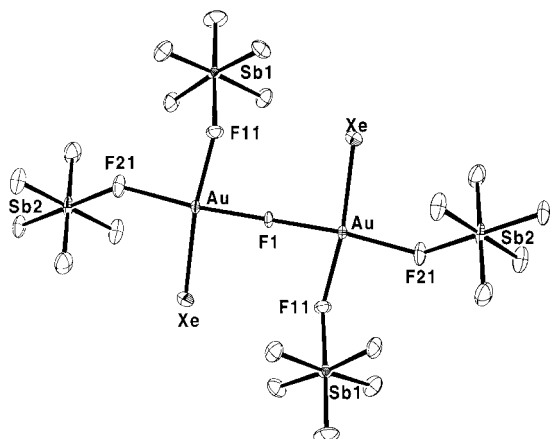


Figure 4. Structure of the  $[\text{Xe-Au-F-Au-Xe}]^{3+}$  ion and its closer anion environment in  $[\text{Au}_2\text{Xe}_2\text{F}^+][(\text{SbF}_6)^-]_3$  (**4**; (ORTEP representation with 50% probability ellipsoids); selected bond lengths [pm]: AuXe 264.7(1), Au–F1 204.5(2), Au–F11 216.6(4), Au–F21 218.9(4), Sb1–F11 194.0(4), Sb2–F21 193.7(4).

square-planar environment, with the Au center coordinated to one Xe atom and three fluorine atoms. The bridging fluorine atom (F1) displays very short distances to gold (204.5213) pm. According to MP2 ab initio calculations this binuclear gold complex should be diamagnetic.<sup>[2]</sup> The intense

Raman bands at  $153$  and  $101\text{ cm}^{-1}$  are assigned to the  $\text{AuXe}$  stretching modes. In the series  $[\text{AuXe}_n]^{2+}$  ( $n = 1–4$ ) only the example for  $n = 3$  is missing.

Another question is why is the  $\text{Au}^{2+}$  ion (a rather rare oxidation state in gold chemistry) so willing to form complexes with xenon, whereas the  $\text{Au}^+$ ,  $\text{Au}^{3+}$ , and  $\text{Au}^{5+}$  ions are not. Although  $[\text{AuXe}]^+$  has been detected in the mass spectrometer as a stable particle,<sup>[3]</sup> our attempts to reduce the  $\text{Au}^{2+}$ –Xe complexes have proved unsuccessful to date. On the other hand we have succeeded in isolating an  $\text{Au}^{3+}$ –Xe complex from a less acidic solution ( $\text{HF}/\text{SbF}_5 \approx 5:1$ ). The ochre-colored crystals are surprisingly stable, and the crystal structure is shown in Figure 5. The gold center again resides in

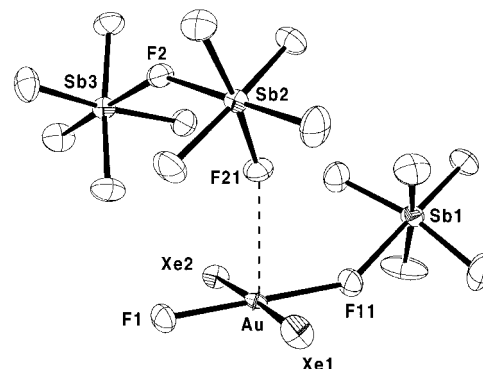


Figure 5. Structure of *trans*- $[\text{AuXe}_2\text{F}]^{2+} [\text{SbF}_6]^- [\text{Sb}_2\text{F}_{11}]^-$  (**5**) (ORTEP representation with 50% probability ellipsoids); selected bond lengths [pm]: Au–Xe1 259.3(1), Au–Xe2 261.9(1), Au–F1 187.8(3), Au–F11 198.1(3), Sb1–F11 206.6(4), Sb2–F21 205.1(4), Au...F21 264.46(5).

a square-planar environment, with the Au atom surrounded by two *trans* Xe atoms and two fluorine atoms. The oxidation state of +3 for Au is not only derived from the stoichiometry (in the single-crystal structure determination undetected H atoms could falsify this result), but also from the bond lengths: The  $\text{Au}^{3+}$ –Xe distances of 259.3(1) and 261.9(1) pm are markedly shorter than the Au–Xe distances in the  $\text{Au}^{2+}$ –Xe complexes, the F–Au distances (187.8(3) and 198.1(3) pm) are typical values for  $\text{Au}^{3+}$ , such as in  $\text{AuF}_3$ .<sup>[4]</sup>

The synthesis of Au–Kr complexes has so far not been achieved. Calculations for the reaction  $[\text{AuXe}_2]^{2+} + 2\text{Kr} \rightarrow [\text{AuKr}_2]^{2+} + 2\text{Xe}$  with relativistically corrected basis sets at the MP2 level gave positive reaction enthalpies of about  $40\text{ kcal mol}^{-1}$ . Since the Au–Xe complexes seem to be at the limit of thermodynamic stability, the outlook for the successful synthesis of Au–Kr complexes is not good.

Further unanswered questions are: Why is it of all the metals that gold is able to act as central atom for these Xe complexes; and is it possible to isolate Xe complexes in solvent systems other than  $\text{HF}/\text{SbF}_5$ , for example in alkanes. The advantage of the  $\text{HF}/\text{SbF}_5$  system is that the concentrations of  $\text{F}^-$  and  $\text{HF}_2^-$  are suppressed to such an extent by acidification that these cannot compete any longer with Xe as ligands.

## Experimental Section

**1:** A poly(perfluoroethylene)–perfluorovinylether copolymerisate (PFA) reaction tube with an internal diameter of 12 mm was filled with  $\text{AuF}_3$



(250 mg, 0.98 mmol) and  $\text{SbF}_5$  (6.8 g, 31 mmol) under exclusion of moisture (dry box,  $<0.1$  ppm  $\text{H}_2\text{O}$ ), and connected to a steel vacuum line whereupon anhydrous HF (1.4 g, 70 mmol) was condensed in. The tube was allowed to warm to room temperature and the components were well mixed (note the  $\text{AuF}_3$  dissolved only slightly in  $\text{HF/SbF}_5$ ). The tube was then cooled to  $-196^\circ\text{C}$  and Xe (1.2 g, 9 mmol) was condensed in, and the tube was sealed. After the tube had been allowed to warm to room temperature (caution: pressure!) a dark red solution formed, from which black-red or light brown dichroic single crystals were obtained on slow cooling to  $-40^\circ\text{C}$ . Raman spectrum (1064 nm,  $-120^\circ\text{C}$ , solid,  $\text{cm}^{-1}$ ):  $\tilde{\nu}=710$  (4), 697 (5), 681 (shoulder), 673 (41), 658 (14), 646 (8), 627 (4), 614 (9), 603 (6), 384 (6), 307 (8), 293 (8), 229 (9), 129 (100).

Crystal structure determination of the tetragonal modification of **1** (for the triclinic modification see reference [1]): With the help of a special device a suitable crystal was mounted on a Bruker-Smart-CCD-1000-TM diffractometer and measured ( $\text{MoK}_\alpha$  radiation, graphite monochromator). Space group  $P4_32_1$  (no. 96),  $a=944.1(1)$ ,  $c=2763.1(5)$  pm,  $V=2463.1 \times 10^6 \text{ pm}^3$ ,  $T=-100^\circ\text{C}$ ,  $Z=8$ , 1800 frames were measured at  $\omega$  distances of  $0.3^\circ$  with 10 s/frame, 9616 measured, 2531 independent reflections, 143 parameters,  $R(F \geq 4\sigma(F))=0.031$ ,  $wR_2=0.060$ . Absorption correction by equilibration of symmetry-related reflections (SADABS). Structure solution and refinement: SHELX programs.<sup>[5]</sup>

**2:** A sample of **1** was cooled to  $-78^\circ\text{C}$ , and the excess xenon was pumped off with the vacuum system. The sample was sealed and warmed to  $5^\circ\text{C}$ ; gas evolution was observed. After slow cooling of the solution to  $-30^\circ\text{C}$ , black, needle-shaped single crystals were formed. Crystal structure determination as described for **1**; space group  $Pna2_1$  (no. 23),  $a=1451.9$ ,  $b=780.9(1)$ ,  $c=1857.2(3)$  pm,  $V=2105.8 \times 10^6 \text{ pm}^3$ ,  $T=-100^\circ\text{C}$ ,  $Z=4$ , 26556 measured, 6445 independent reflections, 263 parameters,  $R(F \geq 4\sigma(F))=0.027$ ,  $wR_2=0.054$ .

**3:** Finely divided gold powder (140 mg, 0.71 mmol), prepared by reducing a  $\text{HAuCl}_4$  solution with  $\text{SO}_2$ , was placed with HF (383 mg, 1.92 mmol),  $\text{SbF}_5$  (1.04 g, 4.8 mmol), and  $\text{XeF}_2$  (120 mg, 0.71 mmol) in a PFA reaction tube. Then Xe was condensed into the tube until a pressure of about 10 bar was reached at room temperature. The solution was initially orange, the gold dissolved very slowly and not completely. Cooling to  $0^\circ\text{C}$  for 12 h resulted in a violet solution from which ochre-colored crystals were obtained at  $-35^\circ\text{C}$ . Raman spectrum (1064 nm,  $-120^\circ\text{C}$ , solid,  $\text{cm}^{-1}$ ):  $\tilde{\nu}=749$  (10), 732 (50), 717 (10), 694 (4), 675 (55), 646 (40), 589 (10), 577 (10), 483 (15), 380 (10), 272 (10), 204 (10), 121 (100). Crystal structure determination as described for **1**; space group  $P\bar{1}$  (no. 2),  $a=560.5(3)$ ,  $b=730.6(4)$ ,  $c=807.6(3)$  pm,  $\alpha=90.99(2)$ ,  $\beta=91.24(2)$ ,  $\gamma=97.86(1)^\circ$ ,  $V=327.42 \times 10^6 \text{ pm}^3$ ,  $T=-100^\circ\text{C}$ ,  $Z=1$ , 5067 measured, 1942 independent reflections, 80 parameters,  $R(F \geq 4\sigma(F))=0.050$ ,  $wR_2=0.133$ .

**4:** Finely divided gold (160 mg, 0.8 mmol),  $\text{XeF}_2$  (137.3 mg, 0.81 mmol), HF (200.4 mg, 10.2 mmol), and  $\text{SbF}_5$  (1.48 g, 6.8 mmol) were placed into a PFA

reaction tube, and subsequently Xe was condensed in. The initial dark green ( $\text{Xe}_2^+$ ) solution soon changed to red-brown at room temperature. The mixture was diluted with more HF to give a ratio of  $\text{HF/SbF}_5$  of about 5:1, whereby gas evolution was observed and the color changed to orange. After the mixture had been cooled to  $5^\circ\text{C}$  for 12 h, a violet solution resulted from which green crystals of **4** were obtained at  $-35^\circ\text{C}$ ; in addition, small amounts of Xe-free gold products were formed. Raman spectrum (1064 nm,  $-120^\circ\text{C}$ , solid,  $\text{cm}^{-1}$ ):  $\tilde{\nu}=750$  (3), 687 (5), 671 (100), 659 (20), 525 (5), 499 (3), 300 (10), 281 (4), 228 (4), 153 (30), 101 (30). Crystal structure determination as described for **1**; space group  $P\bar{1}$  (no. 2),  $a=661.6(1)$ ,  $b=852.8(1)$ ,  $c=925.1(1)$  pm,  $\alpha=72.44(1)$ ,  $\beta=79.27(1)$ ,  $\gamma=67.93(1)^\circ$ ,  $V=459.6 \times 10^6 \text{ pm}^3$ ,  $T=-100^\circ\text{C}$ ,  $Z=2$ , 5695 measured, 2768 independent reflections, 122 parameters,  $R(F \geq 4\sigma(F))=0.030$ ,  $wR_2=0.066$ .

**5:** Au (140 mg, 0.71 mmol),  $\text{XeF}_2$  (120 mg, 0.71 mmol),  $\text{SbF}_5$  (1.0 g, 4.6 mmol), and HF (500 mg, 25 mmol) were allowed to react with Xe (ca. 12 bar) as described for **3**; however, the mixture was only warmed to  $-10^\circ\text{C}$ . A violet solution resulted from which black **1** and ochre-colored **5** crystallized at  $-35^\circ\text{C}$ . Crystal structure determination as described for **1**; space group  $P2_1/c$ ,  $a=795.2(1)$ ,  $b=995.9(2)$ ,  $c=2206.8(4)$  pm,  $\beta=97.11(1)^\circ$ ,  $V=1734.3 \times 10^6 \text{ pm}^3$ ,  $T=-100^\circ\text{C}$ ,  $Z=4$ , 21402 measured, 5292 independent reflections,  $R(F \geq 4\sigma(F))=0.030$ ,  $wR_2=0.055$ .

Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen (Fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-412112 (**1**), CSD-412108 (**2**), CSD-412106 (**3**), CSD-412107 (**4**), and CSD-412109 (**5**).

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# Open-Framework Nickel Succinate, $[\text{Ni}_7(\text{C}_4\text{H}_4\text{O}_4)_6(\text{OH})_2(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$ : A New Hybrid Material with Three-Dimensional Ni–O–Ni Connectivity\*\*

Paul M. Forster and Anthony K. Cheetham\*

Hybrid inorganic–organic compounds are attracting interest as a class of materials that are well suited for the incorporation of transition metals into porous frameworks.<sup>[1, 2]</sup> In such materials, functionality can be introduced from either the inorganic species or the organic linker molecules. Transition metals are well known to confer redox character to zeolitic hosts, and may impart interesting magnetic and spectroscopic properties to porous materials. Organic species, on the other hand, can be used to adjust the channel size, alter the surface of pores, and impart chemical reactivity or chirality.

Much of the current effort on hybrid materials is directed towards synthesizing very open frameworks using rigid organic building blocks. This strategy, as demonstrated by the groups of Robson,<sup>[3]</sup> Yaghi,<sup>[4]</sup> and others, begins with metal atoms or clusters of known geometry and connects them using rigid organic linkages into the desired structure, yielding extended, open networks that often resemble classical high-symmetry inorganic structures. The success of this approach is evidenced by the synthesis of materials with unprecedented porosity<sup>[5]</sup> and large channels containing accessible metal sites.<sup>[6]</sup> However, this approach yields compounds with zero-dimensional metal–oxygen connectivity, which inhibits many of the cooperative effects well known in transition metal oxides.

By contrast, we have explored the synthesis of new hybrid materials containing multidimensional M–O–M frameworks (where M = metal center). Much of the previous work in this area has focused on transition metal vanadate hybrid materials.<sup>[7, 8]</sup> For transition metal carboxylates, several examples of multidimensional metal–oxygen connectivity occur for materials made with linear dicarboxylic acids. Kim and Jung prepared a series of  $\text{Mn}^{\text{II}}$  dicarboxylates (glutaric-1,12 dodecanedicarboxylic acid), all of which exhibit essentially the same structure with one-dimensional (1D)  $\text{MnO}_6$  ribbons.<sup>[9]</sup> An isostructural  $\text{Fe}^{\text{II}}$  adipate<sup>[10]</sup> and a dense, two-dimensional (2D)  $\text{Fe}^{\text{II}}$  succinate<sup>[11]</sup> have also been reported. Férey and co-workers synthesized several cobalt succinates<sup>[12]</sup> based on 2D sheets of edge-sharing  $\text{CoO}_6$  octahedra joined by succinate linkages to form a three-dimensional (3D) framework. One of these materials, MIL-16,<sup>[13]</sup> exhibits good thermal stability

(300 °C) and reversible dehydration/rehydration, which are considered important indications of porosity. These few examples demonstrate that unbranched linear dicarboxylates support the formation of extended M–O–M structures with organic molecules filling at least part of the void space.

We have focused on nickel-containing compounds following our previous successes at synthesizing nickel phosphates with 3D Ni–O–Ni connectivity and good thermal stability.<sup>[14, 15]</sup> In the present work, we describe the synthesis of a nickel succinate. While synthesis of this phase using standard hydrothermal conditions was straightforward, we were unable to obtain single crystals for structural characterization. After many unsuccessful attempts, we adopted a biphasic approach in which succinic acid was dissolved in an organic solvent (cyclohexanol) that is not miscible with water, and water was used to dissolve the nickel source.<sup>[16]</sup> This approach led to single crystals on our first attempt, although it was later recognized that single crystals can only be obtained in a narrow range of synthetic conditions.

The honeycomb structure of nickel succinate is illustrated in Figure 1. To our knowledge, it is the first metal carboxylate with fully 3D M–O–M connectivity. Figure 2 presents one

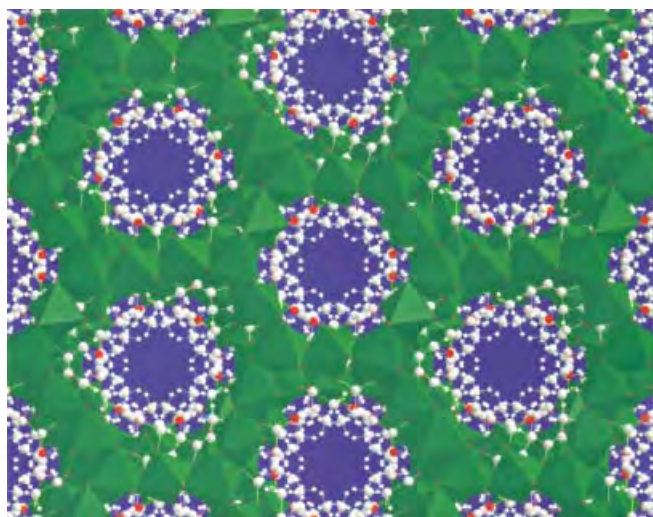


Figure 1. View of the nickel succinate structure down the *c* axis.

unit cell viewed down the *a* axis, and shows that the compound contains layers of edge-sharing  $\text{NiO}_6$  octahedra connected by isolated corner-sharing  $\text{NiO}_6$  octahedra. The layers, shown in Figure 3, consist of 15- and 12-rings of edge-sharing octahedra in a 2:1 ratio. The most prominent feature of the nickel succinate structure is the presence of unidimensional pores running parallel to the *c* axis. The pores are lined almost entirely by the methylene groups of the dicarboxylate, which creates an exceptionally hydrophobic surface. The pores have wide and narrow regions, which can be visualized as two 15-rings capped by narrow 12-ring apertures. There is approximately 4.0 Å between H atoms at these narrow apertures, which implies that the pores are actually a series of open cavities partially blocked every 23 Å. At its widest point, the cavity is 8.0 Å wide (atom to atom). Similar pores

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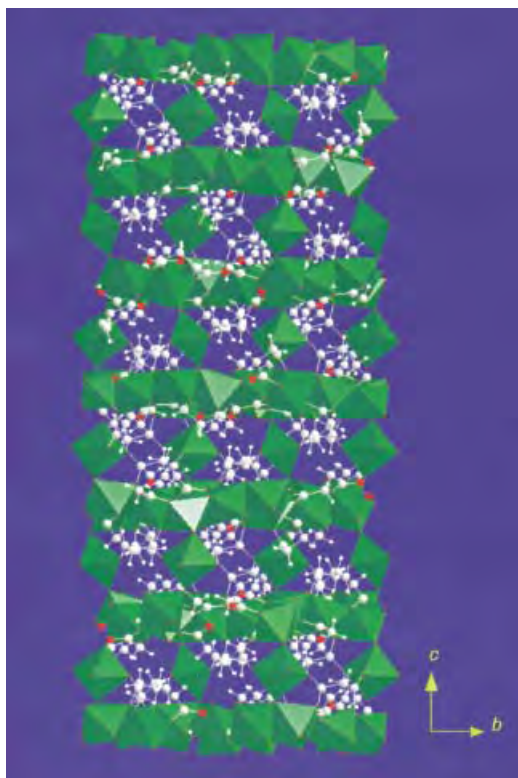


Figure 2. A single unit cell viewed down the *a* axis, with layers containing nickel-oxygen sheets (see Figure 3) apparent. Green: NiO<sub>6</sub> octahedra; red: oxygen.

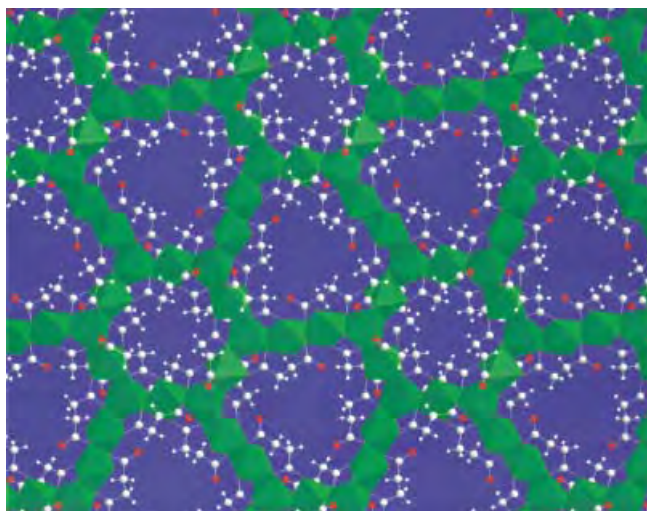


Figure 3. View of a single nickel-oxygen sheet from the *c* axis.

are seen in  $\beta$ -aluminum methylphosphonate.<sup>[17]</sup> We were unable to locate any water of hydration in the pores.

All four crystallographically independent Ni atoms are octahedrally coordinated to oxygen atoms with bond lengths between 2.006 and 2.110 Å and O–Ni–O angles ranging from 78.7 to 102.6°. The three Ni atoms within the layers (Ni(1), Ni(2), and Ni(4), not shown, see the Experimental Section for Cambridge Crystallographic Data Centre supplementary publication number) are coordinated by a combination of carboxylate oxygen atoms, hydroxide ions, and water molecules. For Ni(1), five of the oxygen atoms are associated with

carboxylate groups and the sixth is a hydroxide ion shared between Ni(1), Ni(4), and the nickel between the layers (Ni(3)). In the case of Ni(2), all of the oxygen atoms are from carboxylate groups. For Ni(4), four of the coordination sites are occupied by carboxylate oxygen atoms, while the fifth and sixth sites, which are *trans* to each other, are occupied by the hydroxide anion and a coordinated water molecule directed into the cavity. Ni(3) has *trans* hydroxo ligands, which are shared with nickel atoms in the layers (see above), plus four carboxylate oxygen atoms. There are six carboxylate groups on the three succinate molecules in the asymmetric unit. Five of these groups coordinate to three Ni atoms, while the sixth coordinates with two nickel atoms and has one terminal oxygen atom.

Thermogravimetric analysis (TGA), performed under flowing N<sub>2</sub>, shows a gradual weight loss of 6.0 wt %, which corresponds to the loss of four water molecules per formula unit between 200 and 240 °C. A change from blue-green to light green accompanies the water loss. We attribute this change to the loss of the coordinated water molecule (calcd 3.1 wt %), plus approximately six water molecules per cavity (calcd 3.1 wt %). A sample rehydrated by leaving it in air for several days shows a weight loss in the same region, but with a percentage that corresponds closely to the loss of only coordinated water (observed 2.5 wt %, calcd 3.1 wt %). This weight loss demonstrates that hydration is reversible, which indicates porosity. A weight loss of 50.3 % (calcd 50.8 %) between 380 and 400 °C corresponds to the pyrolysis of the organic component. The single-crystal structure, C,H,N analysis (see Experimental Section), and TGA results exclude the possibility of adsorbed cyclohexanol in the pores and are consistent with the chemical composition: [Ni<sub>7</sub>(C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] · 2H<sub>2</sub>O.

Thermogravimetry, performed under vacuum, shows only small losses in crystallinity through 400 °C, with some peaks remaining until 425 °C. The difference between the TGA and the XRD temperatures may be a result of the differing sample environments. To our knowledge, the decomposition temperature is the highest for any open-framework metal carboxylate. We attribute this exceptional stability to the 3D Ni–O–Ni framework<sup>[18]</sup> of the nickel succinate and to the strong coordination of d<sup>8</sup> Ni centers. The persistence of the parent phase past removal of coordinated water implies the formation of unsaturated metal sites in the dehydrated material. We are currently investigating the nature of these sites.

In spite of the extended Ni–O–Ni connectivity, magnetic susceptibility measurements reveal paramagnetic behavior down to about 5 K, with a magnetic moment of 2.78  $\mu_B$  and a Curie–Weiss temperature  $\theta$  of 4.3 K. Clearly, there is a possibility that the system is magnetically frustrated.

Nickel succinate presents a remarkable 3D Ni–O–Ni framework with porosity and high thermal stability, demonstrating our expectation that multidimensional M–O–M frameworks offer advantages in several respects compared to metal–organic compounds based on isolated metal atoms or clusters. We are continuing to study this interesting phase and have also prepared a related material using glutaric acid,<sup>[19]</sup> details of which will be reported elsewhere.

## Experimental Section

Single crystals: Succinic acid (0.20 g; Aldrich) was dissolved in cyclohexanol (4.0 g; Acros) and carefully layered above water (5.0 g) containing Ni(acetate)<sub>2</sub>·6H<sub>2</sub>O (0.20 g; Alfa Aesar) inside a Teflon autoclave liner (23 mL). The autoclave was heated under autogenous pressure to 150 °C for 3 days and the product, pale blue-green hexagonal platelets, was separated by filtration. Powder samples for physical characterization were prepared in a similar manner by combining Ni(acetate)<sub>2</sub>·6H<sub>2</sub>O (Alfa Aesar), succinic acid (Aldrich), and water in a 1:2:50 molar ratio. In situ X-ray powder diffraction data were collected every 25 °C on a Phillips X-Pert powder diffractometer using CuK $\alpha$  radiation. Elemental analysis (%) calcd: C 24.5, H 2.6; found: C 23.7, H 2.4; the calculation assumes 0.6 surface water molecules per formula unit, as measured by TGA.

Crystal data for [Ni<sub>2</sub>(C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]·2H<sub>2</sub>O, rhombohedral, *R*3̄c, *a* = 21.040(1), *c* = 45.860(4) Å, *V* = 17581(2) Å<sup>3</sup>, *Z* = 18,  $\rho$  = 1.995 Mg m<sup>-3</sup>, *R*<sub>1</sub> = 0.0444 for 3290 reflections, *I* > 4 $\sigma$ *I* for 267 least-squares parameters. Single-crystal diffraction data were collected to 0.75 Å on a clear, hexagonal crystal (0.12 × 0.12 × 0.08 mm) using a Bruker SMART CCD system with MoK $\alpha$  radiation (0.71073 Å). An absorption correction was made using SADABS.<sup>[20]</sup> Lorentz and polarization corrections were made, the structure was solved using direct methods, and the data were refined against |*F*<sup>2</sup>| using the SHELXTL suite.<sup>[21]</sup> All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions with isotropic *U* values 20% higher than the atom to which they were bound. 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-169140. 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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## Icosahedral Virus Particles as Addressable Nanoscale Building Blocks\*\*

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Dedicated to Professor K. Barry Sharpless

Nanochemistry is the synthesis and study of well-defined structures with dimensions of 1–100 nanometers (nm), and thus spans the size range between molecules and materials.<sup>[1]</sup> While supramolecular chemistry (making small molecules bigger) and microfabrication techniques (making big structures smaller) attack from the flanks, biology employs many constructs of this size. Examples include the photosynthetic reaction center, the ribosome, and membrane-bound receptor-signaling complexes, all notable because of their sophisticated yet modular function. The burgeoning field of nanotechnology<sup>[2]</sup> seeks to mimic the information-handling, materials-building, and responsive sensing capabilities of biological systems at the nanometer scale. The special requirements of this enterprise would be well served by building blocks of the proper size with predictable and programmable chemistry.

Cowpea mosaic virus (CPMV) particles are 30 nm-diameter icosahedra, formed by 60 copies of two different types of protein subunits (Figure 1a).<sup>[3]</sup> The physical, biological, and genetic properties of CPMV have been well characterized.<sup>[4]</sup> Approximately one gram of virus is easily and routinely obtained from a kilogram of infected leaves of the black-eye pea plant. The structure of CPMV has been characterized at 2.8 Å resolution by X-ray crystallography and an atomic model of the particle has been constructed.<sup>[5]</sup> The virion displays icosahedral symmetry to the resolution of the crystal structure and an infectious clone of the virus allows site-directed and insertional mutagenesis to be performed in a straightforward and rapid manner.<sup>[6]</sup> The particles are remarkably stable; they maintain their integrity at 60 °C (pH 7) for at least one hour and at pH values from 3.5 to 9 indefinitely at room temperature. Different crystal forms of the virus can be readily produced under well-defined conditions (Figure 1d).<sup>[7, 8]</sup> Here we report on the selective

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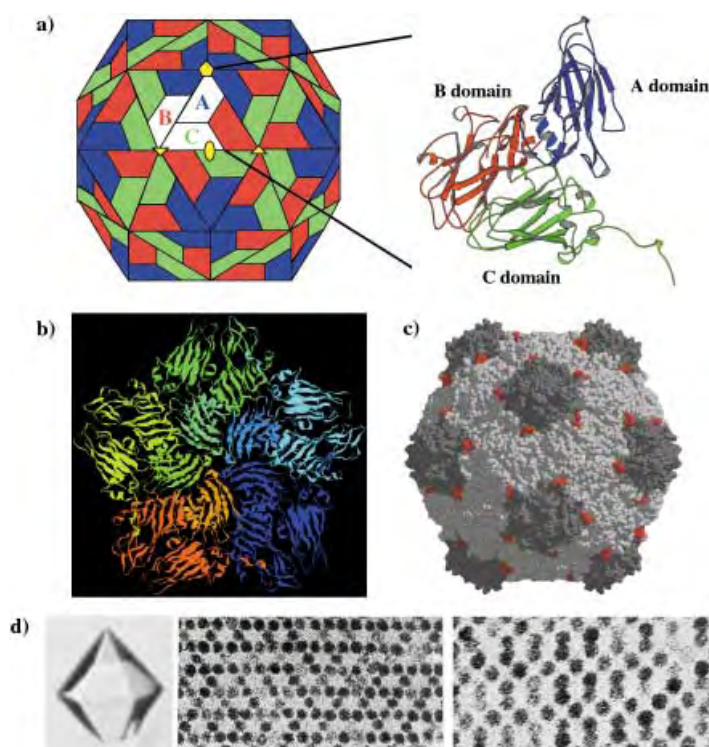


Figure 1. Structure of cowpea mosaic virus and its crystals. a) Left: A diagrammatic representation of CPMV which shows the distribution of the two subunits that comprise the "asymmetric unit", 60 copies of which form the icosahedral particle. The trapezoids in red and green represent the two domains of the large subunit clustered around the threefold symmetry axes and the blue trapezoid represents the small subunit clustered about the fivefold symmetry axes. Right: The folds of the two subunits. b) Organization of five asymmetric units into the "pentamer" centered around a small hole at each fivefold axis. c) Representation of the X-ray crystal structure of CPMV that highlights the EF-loop (in red) in the large subunit in which the cysteine-containing insert is made. d) Left: A hexagonal crystal of CPMV. Electron micrographs of crystals thin sectioned perpendicular to the *c* axis (middle) and the *a* axis (right) showing the remarkably open lattice. Previous studies have shown that proteins with dimensions in excess of 50 Å can be reversibly soaked into the crystals. A typical crystal contains  $10^{13}$  particles.

chemical derivatization of the native virus and the crystal structure of a derivatized particle as well as the preparation of site-specific mutations that allow the attachment of fluorescent dyes and gold clusters through maleimide linkers. The results of these studies demonstrate that the virus particles can be exploited as addressable nanoblocks imbued with a variety of chemical and physical properties.<sup>[9]</sup>

Thiol-selective chemical reagents were used to probe the reactivity of non-disulfide-linked cysteine residues in the native virus particle. The crystal structure shows that CPMV has no free sulfhydryl groups on the outer surface<sup>[5]</sup> and there was no evidence of reaction with the commercially available monomaleimido-Nanogold reagent (Nanoprobes, Inc., Yaphank, NY) that has a molecular diameter of 1.4 nm. However, adducts of the native virus with ethyl mercury phosphate (EMP), an agent with a strong affinity for free sulfhydryl groups but with a dimension of only a fraction of a nanometer, were readily formed. The resulting labeled virus was crystallized under conditions previously employed.<sup>[7]</sup> Crystals with rhombic dodecahedral morphology, identical

to those obtained with native virus, were obtained in four days and X-ray diffraction data to 6 Å resolution were collected on beam line 11–1 at the Stanford Synchrotron Radiation Laboratory. Figure 2a shows a pentamer of the icosahedral constellation of EMP molecules visualized in a difference electron density map. Figure 2b,c shows that the EMP reacted with a single CYS residue at position 295, on the interior surface of the large subunit. This residue contains the sulfhydryl group that appears in the X-ray crystal structure of CPMV to be the most exposed to solvent.<sup>[10]</sup>

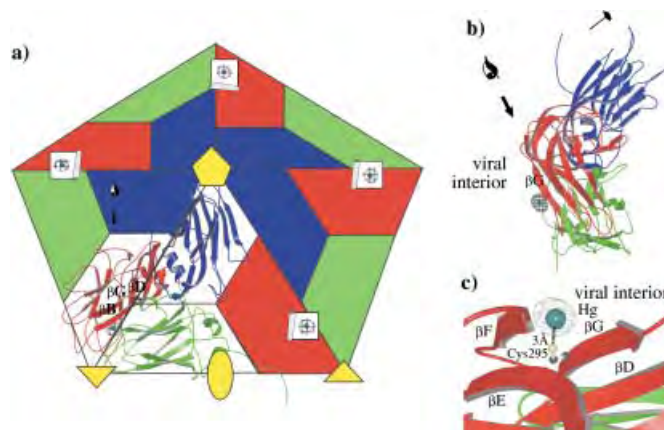
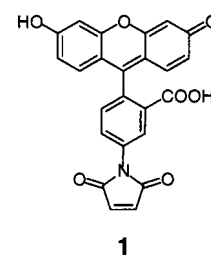


Figure 2. Crystallographic analysis of CPMV particles derivatized with EMP. Amplitudes in the Fourier series calculation were obtained by subtracting structure amplitudes computed from the atomic model of native CPMV from the measured structure amplitudes of the EMP derivative. The difference amplitudes and native phases were used to compute electron density. a) The pentameric assembly of CPMV protein about the fivefold symmetry axis. The difference electron density map reveals bound EMP molecules to be located solely at a single position below the outer capsid surface that corresponds to CYS295; five such sites are shown here. b) A view of the fold of the CPMV asymmetric unit with EMP difference density. c) A close-up view of the position of the EMP difference density.

The reactivity of native CPMV toward an organic thiol-selective reagent was found to be different than toward mercuric ion. Thus, wild-type CPMV was condensed with 5-maleimidofluorescein (**1**). Figure 3 shows a plot of the number of molecules of dye attached to native CPMV as a function of increasing concentration of the dye reagent.<sup>[11]</sup> The curve plateaus at 60 attached dye molecules per particle, which suggests that a single cysteine residue per icosahedral asymmetric unit is most reactive. Denaturing gel electrophoresis analysis of the derivatized protein (Figure 3) showed that the dye is attached exclusively to the *small* subunit, not to the large subunit as was the case for reaction of EMP at CYS295. This alkylation reaction must also occur on the interior capsid surface (see below), but its exact position has not yet been established. Multiple interior cysteine sites, on both small and large subunits, can be addressed with **1** at higher dye-to-subunit ratios without damaging the structural integrity of the particle (data not shown). Small molecules such as **1** are thus apparently able to diffuse through the



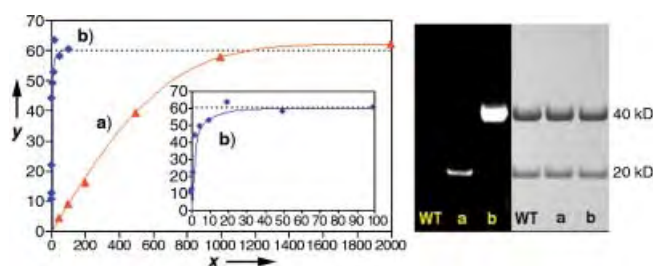
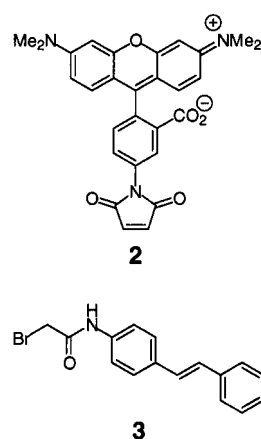


Figure 3. Left: Plots showing the number of the covalently attached fluorescein molecules to (a) native CPMV and (b) the CYS insertional mutant virus as a function of increasing ratio of reagent **1** to virus ( $x$  = equivalents dye–maleimide used per asymmetric unit;  $y$  = dyes attached per particle). Stoichiometries were determined by absorption measurements on solutions of labeled particles by comparison of the intensities of the dye (494 nm) to protein (260 nm), each of which have non-overlapping bands with well-established molar absorptivities. Right: SDS-PAGE analysis: (WT) wild-type CPMV; a) wild-type CPMV-**1** conjugate having approximately 17 dye molecules attached per capsid; b) mutant CPMV-**1** conjugate containing 60 dyes per capsid. On the left (black background) is the gel visualized directly under UV light; this shows the fluorescein emission localized in the small protein subunit of the wild-type virus and the large subunit of the mutant. On the right (light background) is the gel visualized after Coumassie blue staining; this shows both small and large subunits.

capsid, perhaps through the small hole that appears in the crystal structure at each fivefold symmetry axis (Figure 1b).

Mutant CPMV particles were prepared to display sulfhydryl groups on the exterior surface of the structure. Thus, a five-residue insertion containing cysteine (GGCGG) was placed between positions 98 and 99 in the large subunit (Figure 1c). Yields comparable to wild type were obtained with this virus, but the presence of  $\beta$ -mercaptoethanol or tris(2-carboxyethyl)phosphane was required throughout the isolation procedure to avoid crosslinking of particles when they were pelleted by ultracentrifugation or stored after purification. These particles were treated with increasing concentrations of fluorescent dye; the results are shown in Figure 3. In the presence of smaller quantities of the dye–maleimide reagent, up to 60 dye molecules were attached per CPMV virion at significantly faster rates than were observed with the native particle. The reactive interior CYS residue remains active in the mutant particle, such that the two positions can be addressed sequentially under controlled conditions. Thus, reaction with 50 equivalents of **1**, followed by purification and reaction with 1000 equivalents of 5-maleimide tetramethyl-



rhodamine (**2**), gave CPMV decorated with an average of 55 fluoresceins and 49 rhodamines per particle, as determined by UV/Vis spectroscopy.<sup>[11]</sup>

The differential properties of the reactive cysteine residues of wild-type vs. the mutant virus were probed by using the stilbene derivative **3** and antibodies to the stilbene moiety recently developed (Figure 4).<sup>[12]</sup> Since the bromoacetamide group of **3** is selectively reactive with cysteine sulfhydryl groups under condi-

tions similar to those used for maleimides, CPMV–stilbene conjugates were readily prepared and purified for native and mutant virus particles. When treated with antibody 19G2, the presence of an antibody–stilbene complex is revealed by blue fluorescence upon excitation with a hand-held UV lamp; no fluorescence is observed in the absence of either stilbene or antibody. Figure 4 shows the results for intact and denatured CPMV conjugates of **3**. The successful attachment of the stilbene group to both wild-type and mutant CPMV was shown by the appearance of strong fluorescence when the denatured samples were treated with the antibody. The mutant CPMV–**3** conjugate similarly showed antibody binding to stilbene on the intact particle, but the wild-type CPMV–**3** conjugate did not. This is consistent with the attachment of **3** to the interior capsid surface of the wild-type virus, where it is inaccessible to the indicating antibody. In contrast, the mutant virus displays its stilbene-decorated cysteine residues to solvent on the exterior surface.

The mutant virus was also treated with monomaleimido-Nanogold, providing virions displaying absorbance at 420 nm, which indicates attachment of the gold cluster. Derivatized particles were flash frozen and examined by electron microscopy and a three-dimensional image reconstruction was computed (Figure 5a).<sup>[13]</sup> Figure 5b shows a difference map in which density for the model CPMV structure was subtracted from the density computed in the image reconstruction. The gold particles are clearly visible at the positions of the inserted cysteine residues (Figure 5c), providing an example of the installation of chemical structures at designated positions on the icosahedral protein template.

We have shown here for the first time that a virus can function as a convenient and programmable platform for organic chemical reactions. Derivatized CPMV particles will generally display 60 copies of the attached molecule, which makes these systems analogous to very large dendrimers.<sup>[14]</sup> High local concentrations of the attached chemical agent are thereby engineered in the vicinity of the particle, which may result in novel chemical and/or biological properties. Appropriate choices of derivatizing agents can selectively target residues on the inner or outer surface of the particle, which allows double labeling of the particles with different molecules. We are continuing to expand the range of reactivity of CPMV with different mutational insertions and chemical derivatizing agents, with the goal of engineering novel function within a single particle and for aggregates of particles. For example, the virus surface can be patterned with metal nanoparticles if multiple cysteine residues are placed at accessible positions. Such a pattern could potentially



Figure 4. Black-and-white photograph of samples under UV irradiation: A) mutant CPMV-**3** conjugate + stilbene-binding antibody 19G2; B) denatured mutant CPMV-**3** conjugate + 19G2; C) wild-type CPMV-**3** conjugate + 19G2; D) denatured wild-type CPMV-**3** conjugate + 19G2. Note that denaturation causes precipitation of the viral protein, but exposed stilbenes are still recognized by the antibody.



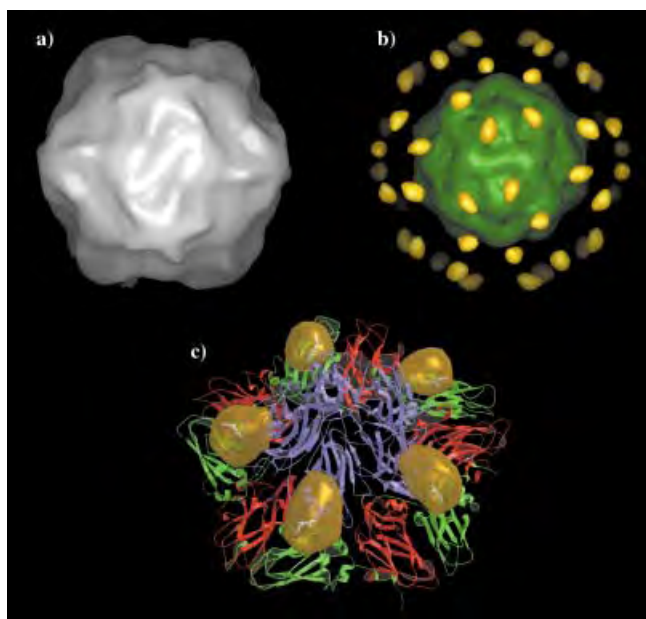


Figure 5. Cryo electron microscopy analysis of derivatized CPMV CYS mutant. a) Three-dimensional reconstruction of CPMV particles at 29 Å resolution labeled with 1.4 nm nanogold clusters. b) Difference electron density map generated by subtracting density computed with the native CPMV X-ray structure from the density shown in Figure 5a. Since the computed native CPMV density was made from only protein, the nucleic acid (shown in green) is visible in the difference map as well as the gold particles. c) A pentameric section of the difference electron density map around the fivefold symmetry axis superimposed on the atomic model of CPMV showing that the gold is attached at the site of the CYS mutation.

be used to form a conducting “wire” at the nanometer scale. Furthermore, CPMV icosahedra show a propensity for self-organization. Straightforward crystallization procedures lead to well-ordered arrays of  $10^{13}$  particles in a typical  $1\text{ mm}^3$  crystal, which may be regarded as a meso scale self-organization of nanoblock components.<sup>[15]</sup> Thus, we believe that CPMV and other viruses have a rich future in applications spanning the worlds of molecular, biological, and materials science.

### Experimental Section

Typical procedure for chemical derivatization of CPMV (unless otherwise noted, “buffer” refers to 0.1M potassium phosphate, pH 7.0): Virus ( $1\text{ mg mL}^{-1}$  in buffer) and maleimide reagent at the indicated concentration were incubated in an 80:20 buffer/DMSO mixture at  $4^\circ\text{C}$  for 6 to 48 h; all reactions contributing to Figure 3 were run for a constant time of 24 h. Reaction mixtures were purified on small scale ( $80\text{ }\mu\text{L}$ ) by passage through short-size exclusion columns prepared with Bio-Gel P-100 Gel (Bio-Rad) in buffer, packed in Bio-Spin disposable chromatography columns, and eluted at  $1000\text{ g}$  for 3 minutes. Multiple passages through freshly-packed columns were performed until dye was undetectable in the wash solution and the relevant absorbance ratios for the virus samples were constant. Purification of larger quantities of derivatized virus was performed by repeated ultracentrifugation pelleting and resuspension in buffer. Yields of labeled virus particles after purification were 70–80%. For quantitation, the “effective” absorptivity ( $\epsilon$ ) of the dye was independently measured by constructing a calibration curve with varying amounts of dye in a buffer solution containing the same concentration of wild-type CPMV as used in the attachment reactions. The experimental error in the number of attached dye molecules is  $\pm 10\%$  of the reported value. The intact nature of the derived particles was substantiated by sucrose gradient ultracentrifugation and size-exclusion FPLC chromatography (Superose-6); non-specific dye adsorption to the virus was ruled out by appropriate control experiments.

Nanogold labeling: Monomaleimido-Nanogold (Nanoprobes, Inc.,  $6\text{ nmol}$ ) was dissolved in 2-propanol ( $10\text{ }\mu\text{L}$ ). The resulting dark brown solution was mixed with the cysteine mutant virus ( $60\text{ }\mu\text{g}$ ) in 0.1M potassium phosphate buffer (pH 6.0,  $90\text{ }\mu\text{L}$ , containing  $10\text{ mM}$  tris(2-carboxyethyl)phosphane). After 20 h at  $4^\circ\text{C}$ , the reaction mixture was purified by passage through size-exclusion gel as described above. The product was collected as a colorless solution ( $100\text{ }\mu\text{L}$ ) with virus concentration  $= 0.45\text{ mg mL}^{-1}$ , which was used directly for the cryo electron microscopy study.

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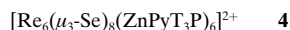
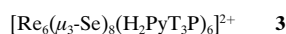
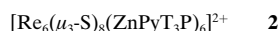
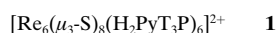
# Octahedral Arrangement of Porphyrin Moieties around Hexarhenium(III) Cluster Cores: Structure of ( $\mu_3$ -Selenido)hexa-(5-(4-pyridyl)-10,15,20-tritolylporphyrin)-hexarhenium(III) ( $2+$ )\*

Ai Itasaka<sup>[+]</sup>, Masaaki Abe, Takashi Yoshimura, Kiyoshi Tsuge, Masamitsu Suzuki, Taira Imamura,\* and Yoichi Sasaki\*

In memoriam Ai Itasaka

Hexanuclear rhenium(III) cluster complexes are the subject of extensive current studies<sup>[1–17]</sup> because of their redox and photoluminescent properties as well as the versatility of the design of the coordination environment around the hexarhenium cores,  $\text{Re}_6(\mu_3\text{-E})_8$  ( $\text{E} = \text{S}, \text{Se}$ ). The cores may be regarded as a giant octahedral center, since the six terminal ligands are oriented in such a manner that each pair of neighboring ligands are arranged vertically to each other. It is possible to mimic the chemistry of simple octahedral metal complexes by using the hexarhenium cluster core, as ligand substitution at the six terminal sites of the core can be controlled with respect to the number and geometrical arrangements of the terminal ligands. Examples are the preparation of a series of pyridine (py) complexes,  $[\text{Re}_6(\mu_3\text{-S})_8\text{Cl}_n(\text{py})_{6-n}]^{(2-n)+}$  ( $n = 2–4$ ), which included the isolation of two isomers (*cis* and *trans*) for  $n = 2$ ,<sup>[4, 13]</sup> and the bridge-chelate formation around the core by a long-chain bidentate ligand,  $(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_6\text{P}(\text{C}_6\text{H}_5)_2$ .<sup>[14]</sup> Another important aspect of using a giant octahedral center is to arrange as many as six sterically bulky ligands around the core, something that is difficult around a single metal center. In the past few years, we have been studying the preparation and properties of some oligomeric porphyrins that are constructed through coordination of pyridylporphyrins to metalloporphyrins.<sup>[18–26]</sup> Although the octahedral arrangement of the porphyrin ligands is interesting as an important structural motif and also as a building block of certain supramolecular complexes, it is too bulky to make stable six-coordinate mononuclear metal complexes. We now show that the octahedral arrangement of porphyrins is possible by using the hexarhenium cores. The new com-

plexes **1–4** ( $\text{H}_2\text{PyT}_3\text{P} = 5\text{-(4-pyridyl)-10,15,20-tritolylporphyrin}$ ) are reported herein.



The complexes **1** and **3** containing free-base porphyrins were prepared by the substitution of 5-(4-pyridyl)-10,15,20-tritolylporphyrin for the solvent molecules in  $[\text{Re}_6(\mu_3\text{-S})_8(\text{CH}_3\text{CN})_6]^{2+}$  and  $[\text{Re}_6(\mu_3\text{-Se})_8(\text{CH}_3\text{CN})_6]^{2+}$ , respectively, in chlorobenzene. Zinc(II) ions were introduced into the porphyrins in **1** and **3** by reacting them with zinc acetate in  $\text{CH}_2\text{Cl}_2$  to give **2** and **4**, respectively.

The structure of **3**-( $\text{SbF}_6$ )<sub>2</sub> was determined by single-crystal X-ray structure analysis.<sup>[27]</sup> Figure 1 shows the remarkable structure of **3**. Six  $\text{H}_2\text{PyT}_3\text{P}$  groups coordinate to the  $[\text{Re}_6\text{Se}_8]^{2+}$  core through the pyridyl group. The bond lengths and angles in the  $[\text{Re}_6\text{Se}_8]^{2+}$  core reveal that the rhenium selenide cluster core has virtually  $O_h$  symmetry as in other hexarhenium chalcogenide complexes.<sup>[3, 7–14, 28–34]</sup> The complex ion has a crystallographically imposed inversion center. In addition, six  $\text{H}_2\text{PyT}_3\text{P}$  groups are arranged essentially in a  $C_3$  manner around the  $[\text{Re}_6\text{Se}_8]^{2+}$  core (Figure 1). Therefore, the complex ion in the crystal has virtual  $S_6$  symmetry. Because the  $\text{H}_2\text{PyT}_3\text{P}$  group itself has  $C_{2h}$  symmetry in the highest symmetrical form and can rotate freely around the  $\text{Re-N}$  bond without mutual steric interactions, the most symmetric structure of the complex ion should be  $D_{3d}$ ,  $D_{2h}$ , or  $D_{2d}$ . The  $S_6$  structure is derived from the  $D_{3d}$  structure by a slight rotation of the porphyrin ligands. Thus, the ideal  $D_{3d}$  structure seems to be distorted by the effect of crystal packing. The cation **3** represents the remarkable class of compounds with six porphyrins in one molecule, the structure of which has been resolved by X-ray structure analysis.

<sup>1</sup>H NMR spectra in  $\text{CDCl}_3$  of the complexes show that all six porphyrin ligands in each complex are equivalent at room temperature. Temperature dependence of the <sup>1</sup>H NMR spectra of **1** is complicated by proton exchange within the porphyrin rings and a possible kinetic rotational barrier of the  $\text{Re-N}$  bond.

Visible absorption spectra of the new complexes in  $\text{CH}_2\text{Cl}_2$  are dominated by strong absorption bands of the porphyrin ligands. All the complexes display a strong Soret band at 422–423 nm with  $\epsilon = 2.5 \times 10^5 \text{ mol}^{-1} \text{ dm}^{-3}$  per ligand, which may be compared with the corresponding band of the free porphyrin at 418 nm ( $\epsilon = 5.0 \times 10^5 \text{ mol}^{-1} \text{ dm}^{-3}$ ). The band in the complexes is somewhat broader than that of the free ligand, which suggests appreciable electronic interactions among the ligands. The four Q bands in the region 500–700 nm were observed for the complexes **1** and **3**, the number of Q bands reduced to two on introduction of  $\text{Zn}^{\text{II}}$  centers into the porphyrin ring (**2** and **4**).

Cyclic voltammograms of the complexes in  $\text{CH}_2\text{Cl}_2$  show the redox waves of the porphyrin moieties in the range  $-2.0$ –

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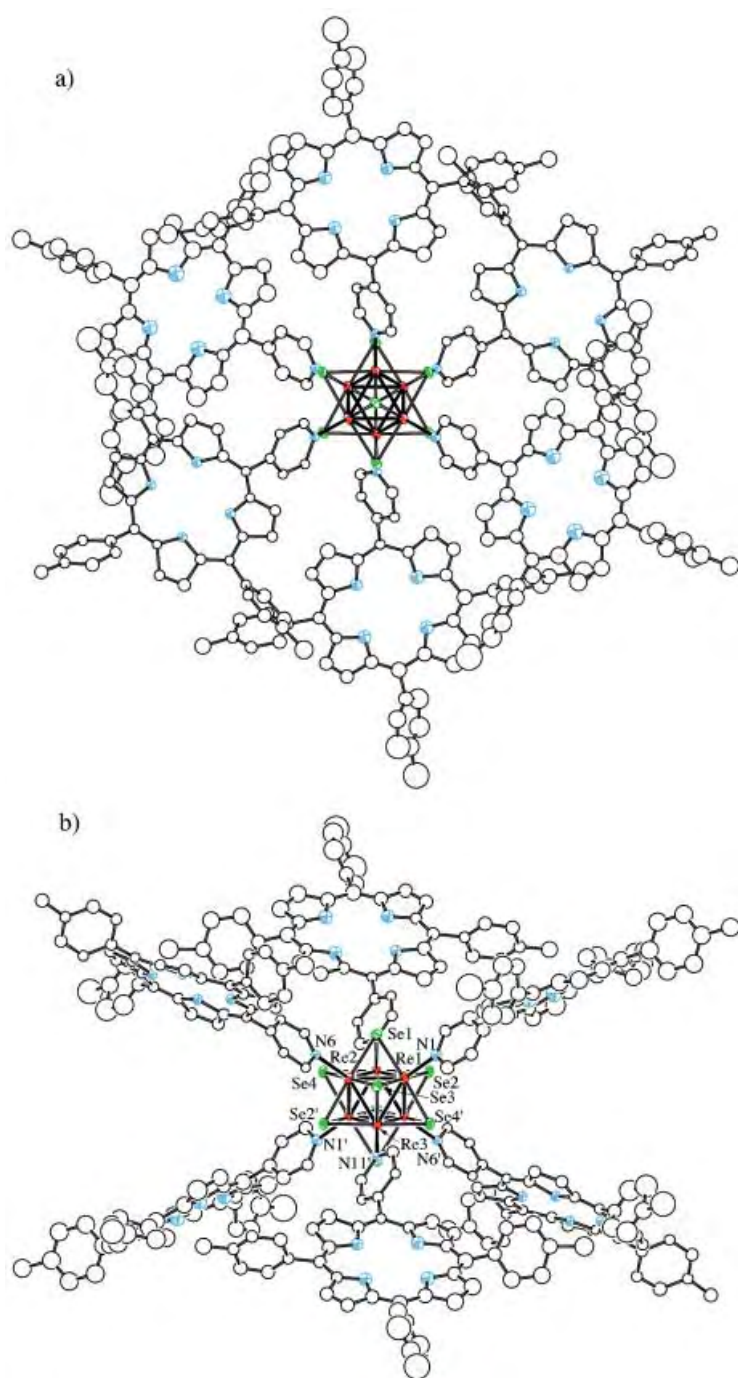
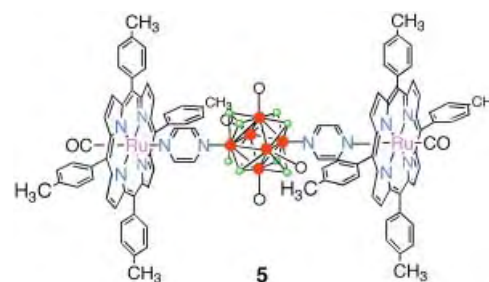


Figure 1. Structure of **3** in  $3 \cdot (\text{SbF}_6)_2 \cdot \text{CH}_2\text{Cl}_2 \cdot 1.6 \text{C}_5\text{H}_{12}$  (ORTEP drawing; thermal ellipsoids at the 30% probability level). a) Top view, b) side view. Red: rhenium, blue: nitrogen, green: selenium. The crystallographically imposed inversion center is at the center of the  $\text{Re}_6$  octahedron. Selected interatomic distances [Å] and bond angles [°] around the central core: Re–Re: 2.571(2)–2.606(2) (av 2.582); Re–Se: 2.486(4)–2.501(3) (av. 2.483); Re–N: 2.14(2)–2.20(3) (av 2.16); Re–Re–Re<sub>(60)</sub>: 59.42(6)–60.76(5) (av 60.00); Re–Re–Re<sub>(90)</sub>: 89.48(7)–90.52(7) (av. 90.00); Re–Se–Re: 62.1(1)–63.4(1) (av 62.7); Se–Re–Se<sub>(90)</sub>: 89.3(1)–90.6(1) (av 90.0); Se–Re–Se<sub>(180)</sub>: 176.4(1)–177.1(2) (av 176.7); Se–Re–N: 90.3(7)–93.1(7) (av 91.7).

+1.7 V versus Ag/AgCl. The redox potentials of the  $\text{Re}^{\text{III}}/\text{Re}^{\text{IV}}$  process for the  $\text{Re}_6(\mu_3\text{-S})_8$  and  $\text{Re}_6(\mu_3\text{-Se})_8$  complexes shift towards positive potentials on increasing the number of pyridyl ligands in place of the terminal halides. The cyclic voltammogram of the  $\text{Re}_6(\mu_3\text{-Se})_8$  complex **3** exhibits a

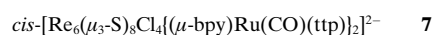
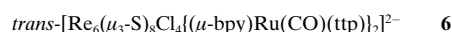
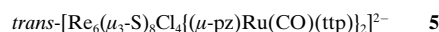
shoulder at the positive side of the porphyrin second oxidation wave at +1.33 V (versus Ag/AgCl), which may be ascribed to the core oxidation.<sup>[4, 13]</sup> The voltammogram of the free ligand displays two reversible reduction waves and one reversible and one irreversible oxidation wave in  $\text{CH}_2\text{Cl}_2$ . Upon coordination of the porphyrin ligand to the hexarhenium core, these waves show only a small shift. The second oxidation wave becomes reversible. There is no sign of the splitting in each wave, which suggests no significant redox interaction among the porphyrin ligands both for the oxidation and the reduction processes. It has been found previously that the hexarhenium core can mediate redox interactions of coordinated ligands as exemplified by the splitting of the reduction waves of the ligands L (4-cyanopyridine, pyrazine, 4,4'-bipyridine, etc.) coordinated to the apices of the hexarhenium(III) core.<sup>[13]</sup> It may be that the perpendicular orientation of the pyridyl group and the porphyrin ring in **1–4** prevents effective redox communication among the porphyrin-ring parts of the six ligands.

We have also prepared new complexes, **5**,<sup>[35]</sup> **6**, and **7** (where  $\text{H}_2\text{ttp}$  = 5,10,15,20-tetra(tolyl)porphyrin; pz = pyrazine; bpy = 4,4'-bipyridine; Scheme 1) in which the



Scheme 1. Schematic structure of **5**.

redox waves of the two ttp ligands do not show any sign of splitting, while those of the bridging pyrazine or 4,4'-bipyridine show small splitting ( $\Delta E = 0.14$  V).<sup>[13]</sup> Here also perpendicular orientation of the bridging pyrazine ligand and the porphyrin ring in **5–7** would be relevant.



Hexarhenium(III) complexes are known to be photo-luminescent.<sup>[3, 5, 6, 13, 14, 16, 36–40]</sup> The new porphyrin complexes **1–4** are also emissive, but the short lifetimes for **3**–( $\text{BF}_4$ )<sub>2</sub> in  $\text{CH}_2\text{Cl}_2$  and the shape of double-maximum emission spectrum suggested that the emission originates from the porphyrin moieties.

The successful arrangement of porphyrin ligands in the octahedral arrangement around the hexarhenium(III) core makes further design of the supramolecular architecture

possible. The work to introduce porphyrins with more than two pyridyl moieties around the hexarhenium(III) core, as well as to bring various metal ions into the porphyrins in the present complexes, is underway.

### Experimental Section

UV/Vis absorption spectra were recorded on a Hitachi U3410 and U3000 spectrophotometer. Cyclic voltammetry was performed with a BAS-50W potentiostat and a software package. The working and counter electrodes were a glassy-carbon disk and a platinum wire, respectively. Cyclic voltammograms were recorded at a scan rate of 100 mV s<sup>-1</sup>. The reference electrode was Ag/AgCl against which the half-wave potential of ferrocene/ferrocenium ion (Fc/Fc<sup>+</sup>;  $E_{1/2}(\text{Fc}^{+/0})$ ) was 0.43 V. <sup>1</sup>H NMR spectra were recorded at 22 °C on a JEOL JNM-EX270 NMR spectrometer.

**1-(BF<sub>4</sub>)<sub>2</sub>**: [Re<sub>6</sub>S<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub><sup>[41]</sup> (100 mg;  $5.58 \times 10^{-5}$  mol) and H<sub>2</sub>PyT<sub>3</sub>P (218 mg,  $3.35 \times 10^{-4}$  mol) were heated under reflux in chlorobenzene (10 mL) for two days (the former was suspended in the solution), and then solvent was removed under reduced pressure. The resulting solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the solution was purified by chromatography on a silica gel column. After the elution of H<sub>2</sub>PyT<sub>3</sub>P with 0.4% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>, the complex cation **1** was eluted with 3% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>. The eluate was evaporated to dryness and the residue was dried in vacuo. Yield: 80 mg (26%); elemental analysis calcd (%) for C<sub>276</sub>H<sub>210</sub>N<sub>30</sub>B<sub>2</sub>F<sub>8</sub>S<sub>8</sub>Re<sub>6</sub>: C 60.34, H 3.85, N 7.65; found: C 60.52, H 4.12, N 7.42; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = -2.73 (s, 12H; NH); 2.68 (s, 36H; CH<sub>3</sub>), 2.70 (s, 18H; CH<sub>3</sub>); 8.85 (s, 24H; H<sub>β</sub>), 9.00 (d, 12H; H<sub>β</sub>), 9.12 (d, 12H; H<sub>β</sub>); 8.09 (d, 36H; *o*-H); 7.54 (d, 36H; *m*-H); 10.47 (d, 12H; 2,6-H of py); 8.69 (d, 12H; 3,5-H of py).

**2-(BF<sub>4</sub>)<sub>2</sub>**: [Re<sub>6</sub>S<sub>8</sub>(H<sub>2</sub>PyT<sub>3</sub>P)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub> (**2**-(BF<sub>4</sub>)<sub>2</sub>; 40 mg;  $7.33 \times 10^{-6}$  mol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and was added to Zn(CH<sub>3</sub>COO)<sub>2</sub>·2H<sub>2</sub>O (9.7 mg;  $4.40 \times 10^{-5}$  mol) dissolved in minimum amount of CH<sub>3</sub>OH. The solution was heated under reflux for 1 h, and was evaporated under reduced pressure. The resulting solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and filtered through Celite. The complex was obtained by diffusing pentane to the solution. Yield: 36 mg (84%); elemental analysis calcd (%) for C<sub>276</sub>H<sub>198</sub>N<sub>30</sub>B<sub>2</sub>F<sub>8</sub>S<sub>8</sub>Zn<sub>6</sub>Re<sub>6</sub>: C 56.43, H 3.40, N 7.15; found: C 56.39, H 3.61, N 7.09; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 2.68 (s, 36H; CH<sub>3</sub>), 2.70 (s, 18H; CH<sub>3</sub>); 8.96 (s, 24H; H<sub>β</sub>), 9.09 (d, 12H; H<sub>β</sub>), 9.19 (d, 12H; H<sub>β</sub>); 8.09 (d, 36H; *o*-H); 7.52 (d, 24H; *m*-H), 7.55 (d, 12H; *m*-H); 10.45 (d, 12H; 2,6-H of py); 8.69 (d, 12H; 3,5-H of py).

**3-(BF<sub>4</sub>)<sub>2</sub>**: [Re<sub>6</sub>Se<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub><sup>[31]</sup> (100 mg;  $4.61 \times 10^{-5}$  mol) and H<sub>2</sub>PyT<sub>3</sub>P (180 mg,  $2.77 \times 10^{-4}$  mol) were heated under reflux in chlorobenzene (5 mL) for 20 h (the former was suspended in the solution), and then the solvent was removed under reduced pressure. The resulting solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the solution was purified by chromatography on a silica gel column. After the elution of unreacted H<sub>2</sub>PyT<sub>3</sub>P with 0.4% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>, **3** was eluted with 3% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>. The eluate was evaporated and the residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/diethyl ether. The purple product was collected by filtration and washed with pentane and then dried in vacuo. Yield: 35 mg (12%); elemental analysis calcd (%) for C<sub>276</sub>H<sub>210</sub>N<sub>30</sub>B<sub>2</sub>F<sub>8</sub>Se<sub>8</sub>Re<sub>6</sub>: C 56.48, H 3.61, N 7.16; found: C 56.59, H 3.87, N 7.03; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = -2.74 (s, 12H; NH); 2.68 (s, 36H; CH<sub>3</sub>), 2.70 (s, 18H; CH<sub>3</sub>); 8.86 (s, 24H; H<sub>β</sub>), 9.00 (d, 12H; H<sub>β</sub>), 9.13 (d, 12H; H<sub>β</sub>); 8.09 (d, 36H; *o*-H); 7.54 (d, 36H; *m*-H); 10.72 (d, 12H; 2,6-H of py); 8.55 (d, 12H; 3,5-H of py).

**3-(SbF<sub>6</sub>)<sub>2</sub>**: This was prepared by using [Re<sub>6</sub>Se<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](SbF<sub>6</sub>)<sub>2</sub> in place of [Re<sub>6</sub>Se<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub><sup>[42]</sup>

**4-(BF<sub>4</sub>)<sub>2</sub>**: [Re<sub>6</sub>Se<sub>8</sub>(H<sub>2</sub>PyT<sub>3</sub>P)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub> (**4**-(BF<sub>4</sub>)<sub>2</sub>; 100 mg;  $1.70 \times 10^{-5}$  mol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and was added to Zn(CH<sub>3</sub>COO)<sub>2</sub>·2H<sub>2</sub>O (22 mg;  $1.02 \times 10^{-4}$  mol) dissolved in minimum amount of CH<sub>3</sub>OH. The solution was heated under reflux for 30 min, and was evaporated under reduced pressure. The resulting solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and filtered through Celite. The solid complex was obtained by diffusing pentane into the solution. Yield: 99 mg (93%); elemental analysis calcd (%) for C<sub>276</sub>H<sub>198</sub>N<sub>30</sub>B<sub>2</sub>F<sub>8</sub>Se<sub>8</sub>Zn<sub>6</sub>Re<sub>6</sub>: C 53.04, H 3.19, N 6.72; found: C 52.76, H 3.35, N 6.59; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 2.67 (s, 36H; CH<sub>3</sub>), 2.71 (s, 18H; CH<sub>3</sub>); 8.96 (s, 24H; H<sub>β</sub>), 9.09 (d, 12H; H<sub>β</sub>), 9.21 (d, 12H; H<sub>β</sub>); 8.09 (d,

36H; *o*-H); 7.53 (d, 24H; *m*-H), 7.55 (d, 12H; *m*-H); 10.71 (d, 12H; 2,6-H of py); 8.57 (d, 12H; 3,5-H of py). ESI-MS:  $m/z$ : 53038 [ $M - 2(\text{BF}_4)$ ]<sup>2+</sup>.

(Bu<sub>4</sub>N)<sub>2</sub>-**5**, (Bu<sub>4</sub>N)<sub>2</sub>-**6**, and (Bu<sub>4</sub>N)<sub>2</sub>-**7**: The pyrazine (pz) complex, (Bu<sub>4</sub>N)<sub>2</sub>-{*trans*-[Re<sub>6</sub>S<sub>8</sub>Cl<sub>4</sub>(pz)<sub>2</sub>]} (20 mg, 0.0093 mmol),<sup>[13]</sup> and [Ru(ttp)(CO)-(CH<sub>3</sub>OH)] (15.4 mg, 0.00186 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The solution was stirred for 1 h at room temperature, toluene (4 mL) was then added, and was left for several days at room temperature to allow for evaporation. Purple crystals were obtained which were collected by filtration and washed with a mixture of CH<sub>3</sub>CN and diethyl ether, and dried in vacuo. Yield of (Bu<sub>4</sub>N)<sub>2</sub>-**5**: 24 mg (69%). The  $\mu$ -4,4'-bipyridine analogues (Bu<sub>4</sub>N)<sub>2</sub>-**6** and (Bu<sub>4</sub>N)<sub>2</sub>-**7** were obtained similarly by using (Bu<sub>4</sub>N)<sub>2</sub>{*trans*-[Re<sub>6</sub>S<sub>8</sub>Cl<sub>4</sub>(4,4'-bipyridine)<sub>2</sub>]} and (Bu<sub>4</sub>N)<sub>2</sub>{*cis*-[Re<sub>6</sub>S<sub>8</sub>Cl<sub>4</sub>(4,4'-bipyridine)<sub>2</sub>]} in place of (Bu<sub>4</sub>N)<sub>2</sub>{*trans*-[Re<sub>6</sub>S<sub>8</sub>Cl<sub>4</sub>(pz)<sub>2</sub>]}.

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- [27] Diffusion of pentane into CH<sub>2</sub>Cl<sub>2</sub> solution of **3**-(SbF<sub>6</sub>)<sub>2</sub> afforded thin fragile crystals, which were carefully mounted on a glass capillary and checked for singularity. Crystal data for **3**-(SbF<sub>6</sub>)<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub>·1.6C<sub>5</sub>H<sub>12</sub> (C<sub>285</sub>H<sub>231.2</sub>N<sub>30</sub>Cl<sub>2</sub>F<sub>12</sub>Re<sub>6</sub>Sb<sub>2</sub>Se<sub>8</sub>):  $M_r$  = 6367.67, triclinic, space group *P*1 (no. 2),  $a$  = 16.510(2),  $b$  = 24.023(5),  $c$  = 24.639(6) Å,  $\alpha$  = 114.596(9),  $\beta$  = 103.752(3),  $\gamma$  = 97.584(4)°,  $V$  = 8330(2) Å<sup>3</sup>,  $Z$  = 1;  $\rho_{\text{calcd}}$  = 1.269 g cm<sup>-3</sup>; crystal dimensions 0.25 × 0.13 × 0.05 mm<sup>3</sup>;  $\mu(\text{MoK}\alpha)$  =

3.27 mm<sup>-1</sup>;  $T = 98$  K,  $2\theta_{\max} = 54^\circ$ . Data were collected on a Mercury CCD area detector coupled with a Rigaku AFC-8S diffractometer with graphite-monochromated MoK $\alpha$  radiation (0.7107 Å) using CrystalClear (Rigaku Co.). Total reflections collected 30371. Data were corrected for Lorentz and polarization effects. An empirical absorption correction was applied by using REQABA (min./max. transmission: 0.61/1.01). The structures were solved on a Silicon Graphics O2 computer system using teXsan, version 1.11 (Molecular Structure Co.). The initial position of rhenium atoms were determined by direct methods and other atoms were located using Fourier and difference Fourier techniques. Re, Sb, and Se atoms were refined anisotropically. Other non-hydrogen atoms were refined isotropically. With the exception of hydrogen atoms of crystal solvents, all hydrogen atoms were located at the calculated positions. One tolyl group was refined by using a rigid model. Full-matrix least-square refinement was employed against  $F$ . Final  $R$  and  $R_w$  values were 0.084 and 0.122 for 8842 observed reflections ( $I > 3.5\sigma(I)$ ) and 735 variable parameters. Max/min. residual electron density were 2.87/–1.60 e Å<sup>-3</sup>, both near Re atoms. 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-170237. 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).

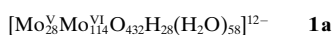
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- [42] [Re<sub>6</sub>S<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](SbF<sub>6</sub>)<sub>2</sub> was prepared by the method used to prepare [Re<sub>6</sub>Se<sub>8</sub>(CH<sub>3</sub>CN)<sub>6</sub>](BF<sub>4</sub>)<sub>2</sub><sup>[31]</sup> but using AgSbF<sub>6</sub> in place of AgBF<sub>4</sub>.

## Photochemical Formation of Tire-Shaped Molybdenum Blues: Topology of a Defect Anion, [Mo<sub>142</sub>O<sub>432</sub>H<sub>28</sub>(H<sub>2</sub>O)<sub>58</sub>]<sup>12-\*</sup>

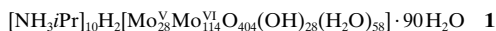
Toshihiro Yamase\* and Petra V. Prokop

UV irradiation (corresponding to the O → Mo ligand-to-metal charge-transfer photoexcitation) of isopolyoxomolybdates in aqueous solutions containing electron donors (such as alkylammonium cations, alcohols, and aliphatic carboxylates) results in formation of high-nuclearity mixed-valence species as a result of reduction self-assembly processes based on the dehydrative condensation at [Mo<sup>V</sup>O<sub>5</sub>(OH)] sites produced photochemically in the polyoxomolybdate lattice.<sup>[1, 2]</sup> [Mo<sub>7</sub>O<sub>24</sub>]<sup>6-</sup> and β-[Mo<sub>8</sub>O<sub>26</sub>]<sup>4-</sup>, which are dominant species at pH levels of 5.4 and 3.3 respectively, are converted into [Mo<sub>14</sub>O<sub>46</sub>]<sup>10-</sup> ({Mo<sub>14</sub>}) = [(Mo<sup>V</sup>Mo<sup>VI</sup>O<sub>23</sub>)<sub>2</sub>]<sup>10-</sup> and [H<sub>14</sub>-Mo<sub>37</sub>O<sub>112</sub>]<sup>12-</sup> = {[H<sub>10</sub>Mo<sup>V</sup>O<sub>40</sub>(Mo<sup>VI</sup>O<sub>2</sub>)<sub>3</sub>][H<sub>2</sub>Mo<sup>V</sup>O<sub>5</sub>O<sub>33</sub>]<sub>2</sub>]<sup>12-</sup>, respectively.

In our extension of the solution photolysis of isopolyoxomolybdates to [Mo<sub>36</sub>O<sub>112</sub>(H<sub>2</sub>O)<sub>16</sub>]<sup>8-</sup> ({Mo<sub>36</sub>}), which is the dominant species at pH 1–2 and higher-Mo concentrations ( $\geq 10^{-2}$  M), we found the photochemical formation of a variety of car-tire-shaped giant molybdenum blues. These were also formed by thermal reduction<sup>[3–8]</sup> of Na<sub>2</sub>MoO<sub>4</sub> with reducing agents such as iron, ascorbic acid, NH<sub>2</sub>OH·HCl, N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>SO<sub>4</sub>, and Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> under strongly acidic conditions (pH ≈ 1). The structure of {Mo<sub>36</sub>} consists of a centrosymmetric arrangement of two {Mo<sub>18</sub>} subunits, each of which is viewed as a Mo<sub>7</sub>O<sub>24</sub> group encircled by edge- and corner-shared MoO<sub>6</sub> octahedra (Figure 1).<sup>[9]</sup> We describe here a diamagnetic blue 28-electron reduced species ({Mo<sub>142</sub>} **1a**) produced photochemically through the degradative self-assembly of {Mo<sub>36</sub>} and discuss size and shape for the ring clusters derived from {Mo<sub>36</sub>} on the basis of the successive two-electron reduction dehydrative–condensation processes similar to the reductive dimerization of [Mo<sub>7</sub>O<sub>24</sub>]<sup>6-</sup> to {Mo<sub>14</sub>}.<sup>[11]</sup>



The title anion (Figure 2a) has been isolated as [NH<sub>3</sub>iPr]<sup>+</sup> salt **1**<sup>[10–12]</sup> the structure of which is quite similar to that reported for Na<sub>26</sub>[Mo<sub>28</sub>Mo<sub>114</sub>O<sub>432</sub>H<sub>14</sub>(H<sub>2</sub>O)<sub>58</sub>]·ca. 300 H<sub>2</sub>O thermally produced in the Na<sub>2</sub>MoO<sub>4</sub>·2 H<sub>2</sub>O/Na<sub>2</sub>SO<sub>4</sub>/N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>SO<sub>4</sub> system.<sup>[4]</sup>



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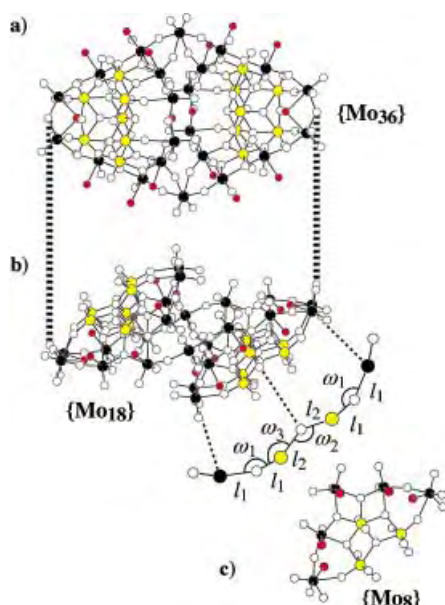


Figure 1. Structure of the  $\{\text{Mo}_{36}\}$  unit (a), which is formed by connecting two  $\{\text{Mo}_{18}\}$  units (b). Curvature of the Mo-O-Mo bond array (b) for the  $\{\text{Mo}_8\}$  block (c) observed in the  $\{\text{Mo}_{18}\}$  unit. For the  $\text{Mo}_7\text{O}_{24}$  moiety: Mo atoms: yellow; aqua-ligand oxygen atoms: red. The edge-shared Mo atoms are black.

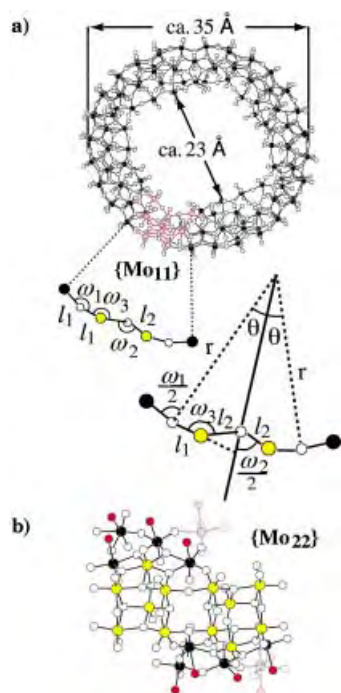
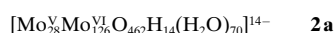
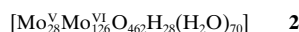


Figure 2. a) Structure of **1a** and curvature of the Mo-O-Mo bond array for the  $\{\text{Mo}_{11}\}$  subunit (red bonds) for estimation of the ring radius. b) Structure of the  $\{\text{Mo}_{22}\}$  unit, formed by connection of two  $\{\text{Mo}_{11}\}$  subunits. For the mono-lacunary  $\text{Mo}_6\text{O}_{23}$  moiety: Mo atoms: yellow; aqua-ligand oxygen atoms: red. Two  $\{\text{Mo}_{11}\}$  linkers are shown with dotted bonds.

The degree of protonation was estimated on the basis of the calculation of the bond valence sums ( $\Sigma s$ ),<sup>[13]</sup> although exact determination of the degree of protonation was a problem. The  $\Sigma s$  calculation for **1a** indicates 28 singly and 58 doubly protonated oxygen atoms. Ten of the singly protonated

oxygen atoms (for  $0.7 \leq \Sigma s \leq 1.2$ ) are  $\mu_3\text{-O}$  atoms situated in the equatorial plane and link two Mo atoms in incomplete double-cubane-type compartments of the mono-lacunary  $\text{Mo}_6\text{O}_{23}$  moieties as well as another Mo atom that also lies in this plane (Figure 2b). The remaining  $\text{OH}^-$  ligands are coordinated at terminal positions to other octahedral Mo sites. Of the doubly protonated O atoms (terminal aqua ligands), 42 aqua ligands are coordinated to the Mo atoms (one aqua ligand per Mo) for three edge-shared octahedra encircling the pentagonal-bipyramidal seven-coordinate Mo site at the each end of 14 mono-lacunary  $\text{Mo}_6\text{O}_{23}$  groups, which are arranged both above and below the ring plane. The remaining 16 aqua ligands are coordinated to 16 corner-shared octahedral Mo sites (one for each) as linkers (Figure 2b). The manometric redox titration shows the presence of 27.5  $\text{Mo}^{\text{V}}$  centers in **1**. Since 10  $[\text{NH}_3\text{Pr}]^+$  ions and 90 crystal water molecules in **1** are determined by X-ray crystallography and the overall number of  $\text{Mo}^{\text{V}}$  centers in **1a** is likely to be 28, the coordination of 28  $\text{OH}^-$  ions and 58 aqua ligands in **1a** (as estimated by the  $\Sigma s$  calculation) enables us to formulate **1** as given (with the additional two protons to balance the charge).

Compound **1a** as a discrete anion is a defect species derived formally by removing six sets of  $[\text{Mo}(\text{H}_2\text{O})\text{O}_2(\mu\text{-O})\text{-Mo}(\text{H}_2\text{O})\text{O}_2]^{2+}$  units ( $\{\text{Mo}_2\}$ ) for the construction of the inner rings from a hypothetical tire-shaped cluster **2**, which consists of 140  $\text{MoO}_6$  octahedra and 14  $\text{MoO}_7$  pentagonal bipyramids, with approximately  $D_{7d}$  symmetry. The half-deprotonated species  $\{\text{Mo}_{154}\}$ , **2a** has been thermally isolated in the  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}/\text{Na}_2\text{S}_2\text{O}_4/\text{HCl}$  system, and the structure of **2a** has been described as a tetradecamer (with approximate  $D_{7d}$  symmetry) of a conjugated group consisting of three different building blocks as  $[\{\text{Mo}_8\} + \{\text{Mo}_2\} + \{\text{Mo}_1\}]$ .<sup>[4, 5]</sup> the  $\{\text{Mo}_8\}$  unit is observed in a quarter moiety of  $\{\text{Mo}_{36}\}$  and neighboring  $\{\text{Mo}_8\}$  units above and below the equator of the ring are linked by a  $\{\text{Mo}_1\}$  unit that lies in the equator (Figure 1 and 2).



Since **2a** is built up by reductive degradation of  $\{\text{Mo}_{36}\}$  to  $\{\text{Mo}_8\}$ , if  $\{\text{Mo}_8\}$  is one of three building blocks, the coordination mode of the  $\{\text{Mo}_8\}$  unit should be retained through the degradation of  $\{\text{Mo}_{36}\}$  (Figure 1c). One can remark that two (as bridging ligands) of five aqua ligands in  $\{\text{Mo}_8\}$  are replaced by  $\mu_3\text{-O}$  atoms lying in the equator for both **1a** and **2a** (Figure 2b).<sup>[4, 5]</sup> In conjunction with that the coordination mode for other three aqua ligands in  $\{\text{Mo}_8\}$  is retained in **1a** (although in some of the  $\text{MoO}_6$  octahedra the terminal O and aqua ligands change their positions), such replacement implies that four  $\text{MoO}_6$  octahedra incorporating the bridging aqua ligands in  $\{\text{Mo}_{18}\}$  are degradatively liberated through the reductive self-assembly reaction of  $\{\text{Mo}_{36}\}$ . Thus, the structure of  $\{\text{Mo}_{154}\}$  could be simply described as a tetradecamer of the  $\{\text{Mo}_{11}\}$  subunits related by  $S_{14}$  symmetry, each of which is the

mono-lacunary  $\text{Mo}_6\text{O}_{23}$  group containing a seven-coordinate Mo site at the end where an additional three edge-shared  $\text{MoO}_6$  octahedra are attached and symmetrically linked by two corner-sharing  $\text{MoO}_6$  octahedra as linkers (Figure 2). In the photochemical formation of  $\{\text{Mo}_{14}\}$  (with the *cis*-configuration of  $\text{Mo}_7\text{O}_{23}$  moieties) as a result of the dimeric condensation of the one-electron reduced species of  $[\text{Mo}_7\text{O}_{24}]^{6-}$  (incorporated in  $[\text{Mo}_{36}]$ ), two electrons are delocalized over the central linear Mo–O–Mo linkages (with Mo–O–Mo bond angles ( $\omega_1$ ) of 174.4 and 175.0° and Mo–O bond lengths ( $l_1$ ) of 1.87–1.89 Å) with approximately  $C_{2v}$  symmetry (Figure 3a).<sup>[1]</sup> In **1a** or **2a**, the Mo–O–Mo bonds linking the neighboring mono-lacunary  $\text{Mo}_6\text{O}_{23}$  groups above and below the equator of the ring have large Mo–O–Mo bond angles ( $\omega_1 = 156$ – $160^\circ$ , average,  $158^\circ$ ) and approximately symmetric Mo–O bonds ( $l_1 = 1.80$ – $1.95$  Å, average, 1.88 Å) (Figure 2a). This let us conceive an idea that in the photo-

the  $\text{MoO}_6$  linker for the inner-ring formation. The partial lack of linkers leads to the formation of a tire-shaped defect structure.

A small curvature of the Mo–O–Mo bonds linking the mono-lacunary  $\text{Mo}_6\text{O}_{23}$  associated moieties for **1a** (Figure 2b) let us estimate both size (the outer O...O diameter,  $D = 2r$ ) and number ( $n$ ) of  $\{\text{Mo}_{22}\}$  building block (as formally four-electron reduced species) for a full-ring construction of  $\{\text{Mo}_{154}\}$ . By using Mo–O–Mo and O–Mo–O bond angles ( $\omega_2$  and  $\omega_3$ , respectively) and Mo–O bond lengths ( $l_2$ ) for the incomplete double-cubane-type compartments above and below the equator, we can estimate a full ring with  $D \approx 34$  Å as a heptamer ( $\{\text{Mo}_{154}\}$ , 28-electron reduced species) of  $\{\text{Mo}_{22}\}$ , since the ring size estimated from  $\omega_1$  ( $156$ – $160^\circ$ , av  $158^\circ$ ),  $\omega_2$  ( $137$ – $145^\circ$ ,  $140^\circ$ ),  $\omega_3$  ( $153$ – $161^\circ$ ,  $157^\circ$ ),  $l_1$  ( $1.80$ – $1.95$  Å,  $1.88$  Å), and  $l_2$  ( $1.95$ – $2.13$  Å,  $2.04$  Å) for **1a** give  $n = 6.5$  and  $D = 31$  Å. The estimated value is very close to  $D \approx 35$  Å for **1a**. On the other hand, in the case where the  $\{\text{Mo}_8\}$  unit (Figure 1c) observed for a quarter moiety of  $\{\text{Mo}_{36}\}$  is a building block for the ring formation, values of  $\omega_1$  ( $151.9$ – $155.7^\circ$ , av  $154.3^\circ$ ),  $\omega_2$  ( $144.0$  and  $141.6^\circ$ ,  $142.8^\circ$ ),  $\omega_3$  ( $155.0$ – $157.6^\circ$ ,  $155.9^\circ$ ),  $l_1$  ( $1.71$ – $1.75$  Å,  $1.73$  Å), and  $l_2$  ( $2.08$ – $2.15$  Å,  $2.12$  Å) for  $\{\text{Mo}_{36}\}$ <sup>[9]</sup> show a large displacement ( $D \approx 24$  Å as a ring corresponding to a pentamer of  $\{\text{Mo}_{22}\}$  unit) from the value for **1a** or **2a**. Furthermore, a curvature (with  $\omega_1 = 174.7^\circ$  (av),  $\omega_2 = 152.6$ – $154.3^\circ$ ,  $153.3^\circ$ ,  $\omega_3 = 156.6$ – $157.8^\circ$ ,  $157.3^\circ$ ,  $l_1 = 1.88$  Å (av), and  $l_2 = 2.13$  Å) of the central Mo–O–Mo bond array for the  $\{\text{Mo}_{14}\}$  building unit (Figure 3a)<sup>[1]</sup> let us estimate a ring of 7.5 units, indicates the plausible construction of either heptamer (with  $D \approx 35$  Å) or octamer (with  $D \approx 40$  Å) of the  $\{\text{Mo}_{14}\}$  unit. The outer size for either full ring by  $\{\text{Mo}_{14}\}$  is also close to that of  $\{\text{Mo}_{154}\}$  or  $\{\text{Mo}_{176}\}$  ( $\equiv [\text{Mo}_{32}^{\text{V}}\text{Mo}_{144}^{\text{VI}}\text{O}_{528}\text{H}_{32}(\text{H}_2\text{O})_{80}]^{7-}$ ). These results strongly suggest that **2a** is built up by the reductive propagation of seven  $\{\text{Mo}_{22}\}$  (or fourteen  $\{\text{Mo}_{11}\}$ ) units (associated with the  $\{\text{Mo}_{14}\}$  formation) rather than by the self-assembly of the three different building blocks as  $[\{\text{Mo}_8\} + \{\text{Mo}_2\} + \{\text{Mo}_1\}]$ . The above mechanism proposed for the formation of tire-shaped molybdenum blues mani-

festes that both  $\{\text{Mo}_{154}\}$  as the heptamer of  $\{\text{Mo}_{22}\}$  units (formally four-electron reduced species) and  $\{\text{Mo}_{142}\}$  as its defect species lacking six pairs of the two  $\{\text{Mo}_1\}$  linkers are 28-electron reduced species. These Mo 4d electrons are diamagnetically delocalized above and below the equator of the ring through Mo–O–Mo linkages (Mo–O–Mo bond angles of  $125$ – $163^\circ$  among corner-shared  $\text{MoO}_6$  octahedra for **1a**).<sup>[14]</sup>

The choice of electron donor, duration of photolysis, and solution pH provide great flexibility with regard to structure within this class of compounds by allowing the tuning of the absence of linkers and the extent of protonation. Molybdenum blue photochemistry provides not only the opportunity to investigate the mechanism of degradation self-assembly processes but also a basis for the molecular design of nanosized ring clusters.

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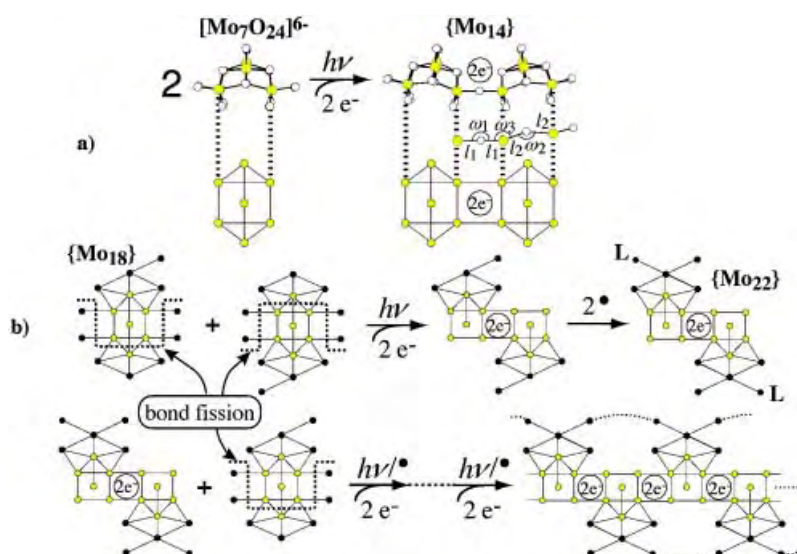


Figure 3. Schematic representations for the photodimerization of  $[\text{Mo}_7\text{O}_{24}]^{6-}$  to  $[(\text{Mo}^{\text{V}}\text{Mo}_6^{\text{VI}}\text{O}_{23})_2]^{10-}$  ( $\{\text{Mo}_{14}\}$ ) (a) and for the photochemical formation of giant tire-shaped clusters from  $\{\text{Mo}_{36}\}$  ( $2\{\text{Mo}_{18}\}$ ) and  $\{\text{Mo}_{22}\}$  (b).  $\text{Mo}_7\text{O}_{24}$ -related moiety Mo atoms are yellow. All the O atoms are omitted for clarity in (b); L = linker.

chemical self-assembly of  $\{\text{Mo}_{36}\}$  ( $=2\{\text{Mo}_{18}\}$ ) to  $\{\text{Mo}_{142}\}$  or  $\{\text{Mo}_{154}\}$  the successive dehydrative condensation of two  $\{\text{Mo}_{18}\}$  halves occurs in a mode similar to the photodimerization of  $[\text{Mo}_7\text{O}_{24}]^{6-}$  to  $\{\text{Mo}_{14}\}$  where the pentagonal-bipyramid-associated moiety is removed from an alternate half of  $\{\text{Mo}_{18}\}$  because of steric hindrance between the bulky moieties, after the liberation of all the  $\text{MoO}_6$  octahedra associated with the bridging aqua ligands (Figure 3b). Then, the attachment of a corner-shared  $\text{MoO}_6$  octahedron (as an additional linker) to each remaining half results in the formation of a  $(\{\text{Mo}_{11}\})_2 \equiv \{\text{Mo}_{22}\}$  unit (two-electron reduced species) which will enable photochemical two-electron reduction again (one-electron reduction for each  $\{\text{Mo}_{11}\}$  subunit). Thus, the successive degradative–dehydration condensation on every two-electron photoreduction continues to build up a ring structure with *trans* orientation of the seven-coordinate Mo-site entities in neighboring  $\{\text{Mo}_{11}\}$  subunits and with further attachment of

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- [10]  $\text{NH}_2\text{Pr}$  (0.68 mL, 8.0 mmol) with  $\text{HClO}_4$  acidification (pH 2.0) was added to a solution of  $\text{Na}_8[\text{Mo}_{36}\text{O}_{112}(\text{H}_2\text{O})_{16}] \cdot 58\text{H}_2\text{O}$  (0.4 g, 0.06 mmol) synthesized according to the method in reference [9], in  $\text{H}_2\text{O}$  (78 mL). Photolysis (two weeks; 500 W superhigh-pressure mercury lamp) of the resulting solution after degassing led to a deep blue solution. After cooling at 4 °C rhombohedral plate crystals of **1**, obtained as uniform crystalline material after 4 weeks, were collected by filtration and dried. Yield: 0.18 g (50% based on Mo), elemental analysis calcd (%): N 0.59, C 1.51, H 1.80; found: N 0.99, C 2.22, H 1.98. The higher N, C, and H values than expected from the given formula are presumably attributed to the high adsorption (corresponding to about six molecules per **1**) of  $[\text{NH}_2\text{Pr}]\text{ClO}_4$  on the highly water-soluble crystalline material of **1**, as suggested by the presence of Cl in the elemental analysis. IR (KBr pellet):  $\tilde{\nu} = 1.618$  (m,  $\delta(\text{H}_2\text{O})$ ), 972(m), 908(w), 746(s), 631(s), 555(s)  $\text{cm}^{-1}$ ;  $\lambda(\text{nm}) = 747$  ( $1.3 \times 10^5 \text{ L mol}^{-1} \text{cm}^{-1}$ ), 1076 ( $1.0 \times 10^5 \text{ L mol}^{-1} \text{cm}^{-1}$ ).
- [11] Space group  $P2_1/n$ ,  $a = 32.316(1)$ ,  $b = 18.021(1)$ ,  $c = 58.618(2)$  Å,  $\beta = 98.388(2)^\circ$ ,  $V = 33771(2)$  Å<sup>3</sup>,  $Z = 2$ ,  $\rho = 2.34 \text{ g cm}^{-3}$ ,  $\mu = 26.4 \text{ cm}^{-1}$ ,  $F(000) = 22560$ . Crystal dimensions  $0.2 \times 0.1 \times 0.02$  mm. Crystal was coated with paraffin oil and mounted in a 20 micron nylon loop material. Intensity data were measured on a Rigaku/MS Mercury CCD diffractometer with graphite-monochromated  $\text{MoK}_\alpha$  radiation ( $\lambda = 0.71071$  Å) at 103 K. Data collection using a  $\omega$  scan at a scan width of  $0.3^\circ$  and  $\chi = 45^\circ$  in five runs (with 600 frames for each) of  $-75.0^\circ < \omega < 105^\circ$ ,  $\phi = 0^\circ$ ;  $-55.0^\circ < \omega < 125^\circ$ ,  $\phi = 0^\circ$ ;  $-55.0^\circ < \omega < 125^\circ$ ,  $\phi = 90^\circ$ ;  $-55.0^\circ < \omega < 125^\circ$ ,  $\phi = 180^\circ$ ;  $-55.0^\circ < \omega < 125^\circ$ ,  $\phi = 270^\circ$ . A crystal-to-detector distance was 95.35 mm. The detector swing angle for the first run was  $15.5^\circ$  and for other runs  $35.5^\circ$ . A total of 78689 reflections was collected of which 325154 unique reflections ( $R_{\text{int}} = 0.098$ ) were used. Lorentz polarization factors were applied and an empirical absorption correction using equivalent reflections was performed with the program ABCOR (T. Higashi, *Program for Absorption Correction*, Rigaku Corporation, Tokyo, **1995**). The structure was solved by direct methods and refined (1817 parameters) by using the TEXSAN software package (SHELXS97) to  $R = 0.094$  for a full-matrix least-squares refinement procedure (29739 unique reflections with  $I > 3\sigma(I)$ ). Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-171234.
- [12] The X-ray powder diffraction (XRD) pattern of **1** shows (002), (010), and (200) peaks at  $d = 30$ , 18, and 16 Å respectively, and an intensive angle peak at  $d = 28$  Å. The latter peak corresponds to one of the diameter spacings (35–23 Å) for the car-tire-shaped ring and seems to be characteristic of the mesostructured nature, since  $\text{Na}_8[\text{Mo}_{36}\text{O}_{112}(\text{H}_2\text{O})_{16}] \cdot 58\text{H}_2\text{O}$  as a starting material gives no low-angle peak at  $2\theta < 5^\circ$  ( $\text{CuK}_\alpha = 1.54056$  Å).
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## Direct Evidence for the Nonrandom Nature of Al Substitution in Zeolite ZSM-5: An Investigation by $^{27}\text{Al}$ MAS and MQ MAS NMR\*\*

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Many important properties of aluminosilicate zeolites, most notably their Brønsted acidity and hence catalytic performance, depend primarily on the framework Al content, that is, the extent of isomorphous substitution of Si by Al. However, even in materials with the same framework structure and composition, the location of catalytically active sites can differ according to the manner in which Al atoms are spatially distributed over the available tetrahedral sites (T-sites) in a given zeolite lattice. Therefore, detailed knowledge of the local ordering of Al atoms in these microporous materials is the starting point for systematically manipulating the distribution of acidic sites within the pore architecture.

Zeolite ZSM-5 (MFI topology) is one of the industrially most important zeolites. It typically crystallizes in the orthorhombic space group  $Pnma$ , and 12 crystallographically distinct T-sites with equal populations exist in the ZSM-5 framework.<sup>[1]</sup> A fundamental, recurring question regarding this type of zeolite structure is whether the acidic sites (that is, Al atoms on T sites) are spatially ordered. Recently, Olson et al.<sup>[2]</sup> carried out Rietveld refinement of synchrotron powder X-ray diffraction (XRD) data on a Cs-ZSM-5 zeolite with 5.8 Al atoms per unit cell ( $\text{Si}/\text{Al} = 15.6$ ) and showed that  $\text{Cs}^+$  ions are located in three different extraframework sites. They speculated that Al atoms may be unequally distributed over the 12 distinct T-sites of the ZSM-5 framework. However, because of the very similar scattering powers of Si and Al for X-rays and the difficulties in obtaining large single crystals, especially at high Al concentrations, it is very difficult, or even impossible, to directly locate Al atoms by conventional diffraction methods. Although many quantum chemical studies have also addressed this issue,<sup>[3]</sup> the nature of

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



the spatial distribution of Al atoms over the 12 ZSM-5 T-sites still remains unresolved, except that there is no strong energetic driving force for nonrandom Al distribution in the ZSM-5 structure. As was earlier indicated by Barrer,<sup>[4]</sup> on the other hand, zeolites are metastable phases that are synthesized hydrothermally under kinetic control. Therefore, if differences in the relative Al substitution energy for each of the 12 T-sites are not too large, the actual Al distributions in real ZSM-5 materials will be strongly influenced by the synthesis conditions. Here we present the results of <sup>27</sup>Al MAS and MQ MAS NMR measurements on a series of as-made ZSM-5 zeolites with 0.4–6.4 Al atoms per unit cell (Si/Al = 250–14) that provide the first direct evidence that the substitution of Al atoms on the T-sites of the ZSM-5 framework during the crystallization process occurs in a nonrandom manner.

Figure 1 shows the <sup>27</sup>Al MAS NMR spectra of a series of as-made ZSM-5 zeolites with different Si/Al ratios. All spectra consist of a two peaks at  $\delta = 51.0$ –51.4 and 52.9–53.9. The same result was also obtained for the <sup>27</sup>Al MAS NMR spectra (not shown) of the corresponding calcined ZSM-5 samples,

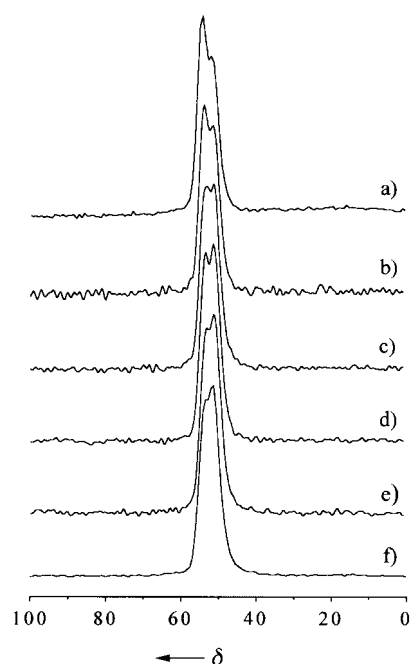


Figure 1. <sup>27</sup>Al MAS NMR spectra of as-made ZSM-5 zeolites with different Si/Al ratios: a) 250, b) 136, c) 79, d) 47, e) 27, and f) 14.

although these two peaks are shifted slightly downfield relative to the as-made samples. Hence, it is clear that the two peaks of each spectrum in Figure 1 result from the presence of at least two crystallographically distinct Al sites in the ZSM-5 framework, rather than arising from possible interactions between the framework Al atoms and encapsulated tetrapropylammonium (TPA) ions.<sup>[5, 6]</sup> Of particular interest is the observation that the intensity ratio of the two peaks for the as-made ZSM-5 samples increases continuously with decreasing Si/Al ratio in the zeolite (Table 1). This suggests that the extent of Al substitution on each of the 12 T-sites in ZSM-5 differs according to the Si/Al ratio of the zeolite synthesis mixture.

A logical next step would be to ascertain whether two or more crystallographically distinct Al sites really contribute to the intensities of the respective peak maxima of the six <sup>27</sup>Al MAS NMR spectra in Figure 1. To answer this question, we carried out <sup>27</sup>Al MQ MAS NMR experiments on all the ZSM-5 samples. Figure 2 shows the 2D <sup>27</sup>Al 3Q MAS NMR

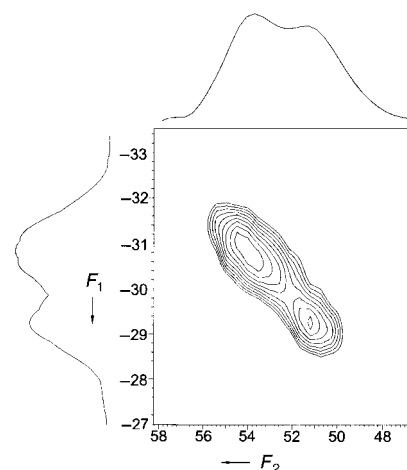


Figure 2. 2D <sup>27</sup>Al 3Q MAS NMR spectrum of an as-made ZSM-5 zeolite with Si/Al = 79 (1.2 Al atoms per unit cell). Two-peak maxima of tetrahedral Al atoms are clearly visible. The corresponding <sup>27</sup>Al MAS NMR spectrum is given at the top of the 3Q MAS NMR plot.

spectrum of an as-made ZSM-5 with Si/Al = 79. In general, the axis  $F_1$  in MQ MAS NMR spectra after appropriate shearing consists of isotropic lines accompanied by second-order quadrupolar shifts for the central transition  $\delta_{QS(1/2)}$ , with their respective anisotropic quadrupolar features on the axis

Table 1. <sup>27</sup>Al MAS NMR chemical shift data for as-made ZSM-5 zeolites with different Si/Al ratios.

| Sample     | Si/Al <sup>[a]</sup> | Al/uc <sup>[a]</sup> | Peak I                        |                               |                               | Peak II                       |                               |                               | Intensity ratio<br>( $A_{II}/A_I$ ) <sup>[e]</sup> |
|------------|----------------------|----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|----------------------------------------------------|
|            |                      |                      | $\delta_{obs}$ <sup>[b]</sup> | $\delta_{iso}$ <sup>[c]</sup> | $C_{Oq}$ <sup>[d]</sup> [MHz] | $\delta_{obs}$ <sup>[b]</sup> | $\delta_{iso}$ <sup>[c]</sup> | $C_{Oq}$ <sup>[d]</sup> [MHz] |                                                    |
| ZSM-5(I)   | 250                  | 0.4                  | 53.9                          | 55.1                          | 1.7                           | 51.4                          | 52.3                          | 1.6                           | 0.73                                               |
| ZSM-5(II)  | 136                  | 0.7                  | 53.5                          | 55.7                          | 1.6                           | 51.1                          | 52.3                          | 1.5                           | 0.80                                               |
| ZSM-5(III) | 79                   | 1.2                  | 52.9                          | 55.4                          | 1.6                           | 51.0                          | 52.3                          | 1.5                           | 1.04                                               |
| ZSM-5(IV)  | 47                   | 2.0                  | 53.1                          | 55.5                          | 1.6                           | 51.0                          | 52.3                          | 1.5                           | 1.11                                               |
| ZSM-5(V)   | 27                   | 3.4                  | 53.0                          | 54.8                          | 1.7                           | 51.0                          | 52.2                          | 1.6                           | 1.20                                               |
| ZSM-5(VI)  | 14                   | 6.4                  | 53.3                          | 54.9                          | 1.7                           | 51.4                          | 52.3                          | 1.6                           | 1.41                                               |

[a] Al atoms per unit cell, determined by elemental analysis. [b] Observed chemical shifts at 9.4 T; the error range is  $\pm 0.3$  ppm. [c, d] Isotropic chemical shifts and second-order quadrupole effects, respectively, estimated from the experimental <sup>27</sup>Al MQ MAS NMR data (for example, see Figure 2). The error range for each  $\delta_{iso}$  is  $\pm 0.3$  ppm, and that for  $C_{Oq}$   $\pm 0.2$  MHz. [e] Determined from curve deconvolution of the <sup>27</sup>Al MAS NMR spectrum of each ZSM-5 sample by using the Origin curve-fitting software.

$F_2$ . This allows us to estimate the distribution of isotropic chemical shift  $\delta_{\text{iso}}$  and second-order quadrupolar effect ( $C_{\text{O}\eta} = C_{\text{O}}(1 + \eta^2/3)^{1/2}$ ) from the spectra, where  $C_{\text{O}}$  and  $\eta$  are quadrupole coupling constant and asymmetry parameter, respectively.<sup>[7]</sup> A close inspection of the tilted, ellipsoidal contours in Figure 2 reveals that their slopes have some distribution, but the average is close to a factor of  $-17/31$  (for  $I = 5/2$ ).<sup>[7b]</sup> This clearly shows that the  $^{27}\text{Al}$  3Q MAS NMR spectrum in Figure 2 consists of overlapped signals from the many sites, whereby differences in  $\delta_{\text{iso}}$  rather than in  $C_{\text{O}\eta}$  are the critical factor governing the spectral pattern. Essentially the same result was observed for the other five as-made ZSM-5 zeolites with different Si/Al ratios. To date, there is one  $^{27}\text{Al}$  MQ MAS NMR study on ZSM-5 that showed tilted contours similar to those in Figure 2.<sup>[7a]</sup> However, the interpretation of the spectra differed from our analysis.

Although structural data on as-made ZSM-5 zeolites are not currently available in the literature for the entire Si/Al range studied here, the detailed crystal structures of two as-made samples with Si/Al = 86 and 11.9 were determined by single-crystal X-ray diffraction.<sup>[8]</sup> Since the Si/Al ratios of these two zeolites are similar to those of ZSM-5(III) and ZSM-5(VI), respectively (Table 1), we attempted to simulate their  $^{27}\text{Al}$  3Q MAS NMR spectra using the reported crystallographic data and compared the results with the experimental spectra of ZSM-5(III) and ZSM-5(VI). Table 2 lists  $\delta_{\text{iso}}$ ,  $C_{\text{O}}$ , and  $\eta$  for the 12 possible Al sites in an as-made ZSM-5 with Si/Al = 86, calculated from the crystallographic data of Olson et al.<sup>[8a]</sup> by using the equation of Lippmaa et al.<sup>[9]</sup> and the point-charge model.<sup>[10]</sup> The  $C_{\text{O}\eta}$  and  $\delta_{\text{QS}(1/2)}$  values calculated from  $C_{\text{O}}$  and  $\eta$ <sup>[7b]</sup> are also given in Table 2. With the  $\delta_{\text{iso}}$  and

$\delta_{\text{QS}(1/2)}$  data, in turn, shifts of center of gravity on the axes  $F_1$  and  $F_2$  ( $\delta_{\text{CG1}}$  and  $\delta_{\text{CG2}}$ ) were determined,<sup>[7b]</sup> and the 3Q MAS NMR spectrum of an as-made ZSM-5 with Si/Al = 86 was finally simulated with the 12 sets of  $\delta_{\text{CG1}}$  and  $\delta_{\text{CG2}}$  data (Figure 3). The overall scattering pattern of the data and the chemical shift ranges in this simulated spectrum match well

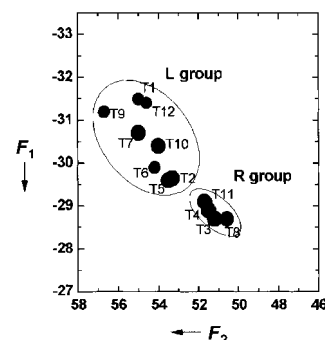


Figure 3.  $^{27}\text{Al}$  3Q MAS NMR spectrum of an as-made ZSM-5 sample with Si/Al = 86 (1.1 Al atoms per unit cell), simulated by using the calculated  $\delta_{\text{CG1}}$  and  $\delta_{\text{CG2}}$  values in Table 2. The dot sizes represent the expected intensity of the 12 possible Al sites with different  $C_{\text{O}\eta}$  values listed in Table 2, which are assumed to have equal populations.

with those of the experimental spectrum (Figure 2) of the ZSM-5(III) sample with Si/Al = 79. A quite similar result was obtained for the comparison of the simulated 3Q MAS NMR spectrum of as-made ZSM-5 with Si/Al = 11.9 and the experimental spectrum of ZSM-5(VI) (see Supporting Information). Figure 3 also shows that the expected intensities are not the same for the 12 possible Al sites with different  $C_{\text{O}\eta}$  values (Table 2), although they are assumed to have equal populations, since the intensity of MQ MAS NMR lines is a function of  $C_{\text{O}\eta}$ .<sup>[7a, 11]</sup> Thus, the fact that the intensity pattern in Figure 3 differs from that in Figure 2 could be another indication of nonrandom Al distribution over the 12 ZSM-5 T-sites. If the 12 NMR lines indicated in the simulated spectrum are merged into two sets of contours like those found in the experimental spectrum, on the other hand, they can be divided into R and L groups, that is, sites T3, T4, T8, and T11 with a range of average T-O-T angles between 158.7 and 160.6° on the right, and the other eight T-sites, with a range of average T-O-T angles between 150.4 and 156.4°, on the left.<sup>[8a]</sup> From the  $C_{\text{O}\eta}$  values listed in Table 2, the average  $C_{\text{O}\eta}$  parameters for the R and L groups were calculated to be 1.19 and 1.21 MHz, respectively. These values are in reasonable agreement with the experimental values for the two peaks in the  $^{27}\text{Al}$  MAS NMR spectrum of ZSM-5(III) (see Table 1), and this is further support for the reliability of the simulation. Since the intensity ratio of the two peaks in Figure 1 decreases with increasing Si/Al ratio in the zeolite,<sup>[12]</sup> the Al atoms in ZSM-5 samples with a lower Si/Al ratio (probably <50) are preferentially located on T-sites with larger T-O-T angles, and vice versa in zeolites with higher Si/Al ratios.

In conclusion, we have demonstrated that the preference of Al atoms for particular T-sites in as-made ZSM-5 zeolites depends strongly on the framework Si/Al ratio, that is, the extent of Al substitution, although some differences could

Table 2. Calculated NMR parameters for Al atoms in the 12 distinct T-sites of an as-made ZSM-5 with Si/Al = 86 (1.1 Al atoms per unit cell).

| Possible Al site | $\delta_{\text{iso}}$ [a] | $C_{\text{O}}$ [MHz] <sup>[b]</sup> | $\eta$ [c] | $C_{\text{O}\eta}$ [MHz] <sup>[d]</sup> | $\delta_{\text{QS}(1/2)}$ [e] | $\delta_{\text{CG1}}$ [f] | $\delta_{\text{CG2}}$ [g] |
|------------------|---------------------------|-------------------------------------|------------|-----------------------------------------|-------------------------------|---------------------------|---------------------------|
| T1               | 56.6                      | 1.59                                | 0.62       | 1.70                                    | -1.58                         | -31.5                     | 55.0                      |
| T2               | 53.8                      | 0.88                                | 0.49       | 0.91                                    | -0.46                         | -29.6                     | 53.3                      |
| T3               | 52.1                      | 0.79                                | 0.80       | 0.87                                    | -0.42                         | -28.7                     | 51.2                      |
| T4               | 52.3                      | 1.14                                | 0.51       | 1.20                                    | -0.78                         | -28.9                     | 51.5                      |
| T5               | 53.8                      | 0.70                                | 0.85       | 0.78                                    | -0.34                         | -29.6                     | 53.5                      |
| T6               | 54.4                      | 1.55                                | 0.47       | 1.60                                    | -0.21                         | -29.9                     | 54.2                      |
| T7               | 55.6                      | 0.97                                | 0.81       | 1.10                                    | -0.63                         | -30.7                     | 55.0                      |
| T8               | 51.7                      | 1.35                                | 0.40       | 1.40                                    | -1.06                         | -28.7                     | 50.6                      |
| T9               | 56.8                      | 0.49                                | 0.51       | 0.51                                    | -0.14                         | -31.2                     | 56.7                      |
| T10              | 54.9                      | 1.23                                | 0.44       | 1.30                                    | -0.89                         | -30.4                     | 54.0                      |
| T11              | 52.6                      | 1.23                                | 0.29       | 1.30                                    | -0.86                         | -29.1                     | 51.7                      |
| T12              | 56.3                      | 1.61                                | 0.82       | 1.80                                    | -1.75                         | -31.4                     | 54.6                      |

[a] Isotropic  $^{27}\text{Al}$  chemical shifts calculated from the average T-O-T angles of the 12 distinct T-sites in an as-made ZSM-5 with Si/Al = 86 (1.1 Al atoms per unit cell), reported by Olson et al.,<sup>[8a]</sup> by using the equation of Lippmaa et al.<sup>[9]</sup> [b] Quadrupole coupling constants calculated from the coordinates of the four nearest oxygen atoms of each T-site, given by Olson et al.,<sup>[8a]</sup> by using the point-charge model.<sup>[10]</sup> [c] Asymmetry parameters calculated by the same method described in [b]. [d] Second-order quadrupole effects ( $C_{\text{O}}(1 + \eta^2/3)^{1/2}$ ) calculated by using the  $C_{\text{O}}$  and  $\eta$  values listed in this table. [e] Second-order quadrupolar shifts of the central transition calculated from  $C_{\text{O}\eta}$  in this table by using Equation 26c in ref. [7b]. [f] Shifts of center of gravity on the  $F_1$  axis of a simulated 3Q MAS NMR spectrum, calculated from the  $C_{\text{O}\eta}$  and  $\delta_{\text{iso}}$  values given in this table by using Equation 70 in ref. [7b]. [g] Shifts of center of gravity on the  $F_2$  dimension of a simulated 3Q MAS NMR spectrum, calculated by using Equation 71 in ref. [7b].

exist between zeolites synthesized in hydroxide and fluoride media in this respect. Further study is necessary to determine the underlying mechanisms of this intriguing behavior. However, the overall NMR results presented here strongly suggest that the substitution of Al atoms into the ZSM-5 framework during the crystallization process may be kinetically, rather than energetically, controlled. This led us to believe that the substitution patterns of other heteroatoms (e.g., B, Ga, Ti, etc.) in the ZSM-5 framework would also be nonrandom, although they may differ in manner from Al substitution. In fact, recent neutron powder diffraction studies on TS-1, the titanosilicate analogue of ZSM-5, showed that Ti atoms are not uniformly distributed over the 12 ZSM-5 T-sites.<sup>[13]</sup> Finally, it is of interest whether our concept can be applied to other important high-silica materials with multiple T-sites such as zeolites  $\beta$  and MCM-22.<sup>[1]</sup>

### Experimental Section

Six ZSM-5 zeolites with different Si/Al ratios were synthesized by using  $\text{NH}_4\text{F}$  (+98%, Aldrich) and  $\text{TPABr}$  (98%, Aldrich) in fluoride media to minimize the possible influence of connectivity defects on the distribution of Al in the ZSM-5 framework, according to procedures described elsewhere.<sup>[14]</sup> The Si/Al ratio in the final product was varied by adjusting the amount of  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  (99%, Wako) that was added to the synthesis mixture as Al source. Amorphous silica (Aerosil 200, Degussa) was used as Si source. All ZSM-5 zeolites prepared here were phase-pure and highly crystalline (powder XRD, Rigaku Miniflex,  $\text{CuK}\alpha$  radiation). The Si/Al ratios of these six as-made samples were analyzed in the Analytical Laboratory of KIST. The absence of any detectable line at  $\delta \sim 0$  in the  $^{27}\text{Al}$  MAS NMR spectra (Figure 1) indicates that all the Al atoms in these samples are isomorphously incorporated into the T-sites of the ZSM-5 framework. Also, thermogravimetric and differential thermal analyses (TA Instruments SDT 2960) reveals that they contain 3.8–4.3 TPA cations per unit cell.

The  $^{27}\text{Al}$  MAS NMR spectra were recorded on a Bruker DSX 400 NMR spectrometer that operates at a  $^{27}\text{Al}$  frequency of 104.27 MHz and a spinning rate of 13 kHz. The spectra were obtained by acquisition of 300–400 pulse transients, which was repeated with a  $\pi/12$  rad pulse length of 0.8  $\mu\text{s}$  and a recycle delay of 1 s. The  $^{27}\text{Al}$  chemical shifts are referenced to a 1N  $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$  solution. The 2D  $^{27}\text{Al}$  3Q MAS NMR spectra were recorded on a Varian INOVA 400 NMR spectrometer by the two-pulse z-filtered procedure with rotor synchronization<sup>[15]</sup> at a spinning rate of 10 kHz, with an excitation pulse of 6  $\mu\text{s}$  and a conversion pulse of 1.8  $\mu\text{s}$  for an rf field strength of 84 kHz. For each  $t_1$  384 or 768 scans were accumulated, and  $t_1$  was incremented 64 times.

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## A New Approach to Osmium-Catalyzed Asymmetric Dihydroxylation and Aminohydroxylation of Olefins\*\*

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Osmium-catalyzed asymmetric dihydroxylation (AD) of olefins using cinchona alkaloid derived ligands is known for its exceptional scope and reliability across nearly the entire

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range of olefin types and substitution patterns on both laboratory and industrial scales.<sup>[1]</sup> Its sister reaction, the asymmetric aminohydroxylation (AA), is the aza-analogue of the parent transformation and represents a powerful, direct route to vicinal amino alcohols.<sup>[2]</sup> After its discovery in 1996, a great deal of effort has been devoted to make it as reliable, versatile, and convenient to use as its dihydroxylation counterpart. Although the AA process has already found substantial use in organic synthesis, it still lacks the generality and reliability of the AD process. In many cases, problems arise that appear to be related to some combination of the following issues: 1) selectivities (chemo-, regio-, and enantio-), 2) substrate scope, and 3) catalyst activity. Of these, chemoselectivity is the most serious, with up to 70% of corresponding vicinal diol being produced in unfavorable cases.

A uniquely helpful mechanistic insight about these osmium(VIII)-catalyzed systems arose during our process improvement endeavors on the AD—namely, there are two catalytic cycles producing the diol (Scheme 1).<sup>[3]</sup> Under homogeneous conditions, where the reoxidant has constant access to all the catalytic intermediates, the turnover is locked into the second cycle, simply because hydrolysis steps ( $h^1$  and  $h^2$ ) are *much slower* than the redox steps ( $r^1$ ,  $r^2$ , and  $r^3$ ). As a consequence, the osmium(VI) bis(glycolate) (**II**) is the resting form of the catalyst.

In the last few years, we have discovered that certain classes of olefins give extraordinary results when subjected to the standard reaction conditions for either the osmium-catalyzed dihydroxylation or aminohydroxylation process.<sup>[4, 6]</sup> In the absence of the alkaloid ligand, and even with very low catalyst loadings, these special olefins undergo rapid and nearly quantitative conversion to the expected products, vicinal diols or amino alcohols. This is in sharp contrast to other olefins, whose turnover is crucially dependent on the ligand-acceleration effect.<sup>[5]</sup> Having recently found that unsaturated carboxylic acid<sup>[6]</sup> substrates constitute an extreme example, even within this “special” reactivity zone, we redoubled

efforts to get at the mechanistic underpinnings which account for such phenomenally vigorous catalysis.

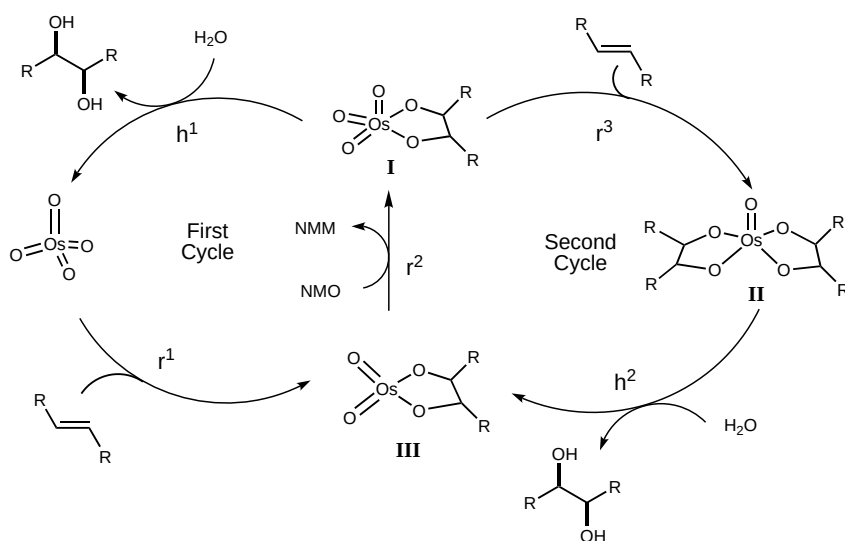
With all the “special” substrates only racemic products are formed, even when an enormous excess of the chiral ligand is added. This and other available evidence<sup>[7]</sup> strongly suggest that these olefins turnover almost exclusively in the second catalytic cycle, in which osmium(VI) bis(glycolate) (**II**) (or the bis(azaglycolate) in the case of aminohydroxylation) is the most stable intermediate—it is so stable that it is the only detectable osmium complex present under steady-state conditions. According to our current mechanistic hypothesis, the resident carboxylate groups ( $-\text{COO}^-$ ) in this complex facilitate the rate-determining step, hydrolysis, thereby accounting for the dramatically increased reactivity of these substrates.

Although we had traditionally sought to avoid the second cycle at all costs, deleterious as it is to enantioselectivity, the enticing possibilities it offers for a new way to control osmium(VIII) catalysis have been clear since the time of its discovery in 1982. Although early attempts to obtain enantioselectivity with second-cycle ligands failed, the recent enormous jump in effectiveness of the second-cycle systems<sup>[6]</sup> convinced us that their inherent advantages *must* be exploited to develop new catalytic processes. To tame the second cycle, one needs to design a ligand that a) is chiral and capable of controlling stereochemistry in the olefin oxidation step  $r^3$ ; b) aids in the hydrolytic release ( $h^2$ ) of the diol from the initial  $\text{Os}^{\text{VI}}$ -product complex (**II**); and c) is not itself hydrolytically removed from the osmium coordination sphere.<sup>[8]</sup>

Herein, we describe the first ligands found to induce asymmetry in the osmium-catalyzed dihydroxylation and aminohydroxylation proceeding in the second catalytic cycle. As a simple model for screening the ligand candidates shown in Table 1, we have chosen the dihydroxylation of styrene under the Upjohn conditions.<sup>[9]</sup> Incidentally, overoxidation of the product diol, a fairly common side reaction in the Upjohn dihydroxylation, was not observed.

Even tartaric acid, although needed in quantity of 25 mol %, showed asymmetric induction. Finding ligands with a higher affinity for osmium was an obvious requirement to reduce the amount of ligand. Since *N*-sulfonyl-1,2-hydroxyamines (vicinal hydroxysulfonamides) have much higher binding constants for osmium than analogous 1,2-diols, a number of *N*-toluenesulfonyl derivatives of  $\alpha,\beta$ -hydroxy-amino acids were screened resulting in the improvement of the enantiomeric excess (*ee*) to 42%. The *ee* values remained constant throughout the course of reactions and, more importantly, as little as 1.5–2 mol % ligand was sufficient to attain the ceiling enantioselectivity (Figure 1).<sup>[10]</sup>

Simple structure–activity studies have revealed that a free carboxylate group appears to be an essential component of a successful ligand. Thus, only racemic diol was obtained when the methyl ester of **1** was used as a ligand. Location of the HO and TsNH groups was found to play an



Scheme 1. The two catalytic cycles in the osmium-catalyzed dihydroxylation of olefins using 4-methylmorpholine-*N*-oxide (NMO) as reoxidant.

Table 1. Dihydroxylation of styrene with novel ligands.<sup>[a]</sup>

| Entry | Ligand | Ligand [mol %] | Conversion [%] | ee [%] (abs. conf.) <sup>[b]</sup> |
|-------|--------|----------------|----------------|------------------------------------|
| 1     |        | 5              | > 99           | 25 (R)                             |
| 2     |        | 2              | > 99           | 25 (R)                             |
| 3     |        | 5              | > 99           | 7 (R)                              |
| 4     |        | 5              | > 99           | 29 (R)                             |
| 5     |        | 5              | > 99           | 42 (R)                             |
| 6     |        | 2              | > 99           | 42 (R)                             |
| 7     |        | 5              | > 99           | 5 (R)                              |
| 8     |        | 5              | > 99           | 25 (S)                             |

[a] All reactions were performed on 1 mmol scale at 0.5 M concentration in *t*BuOH/H<sub>2</sub>O (1:1) with 1.1 equiv NMO and 0.2 mol % of OsO<sub>4</sub>. The progress was monitored by GC, and *ee* values were determined by HPLC (Chiralcel OB, 10% *i*PrOH/Hexane). [b] The absolute configuration of styrene diol was assigned by comparison with authentic samples.

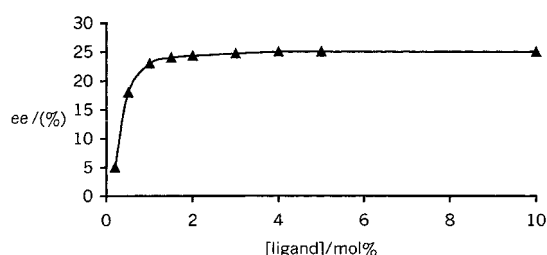


Figure 1. Dependence of enantioselectivity on ligand concentration in dihydroxylation of styrene with **1** as a ligand.

important role as well. For example, the phenylisoserine-based ligand **1** afforded a higher *ee* value than its regioisomer **2**. The absolute configuration of the diol product appears to be determined by the stereochemistry of the  $\alpha$ -carbon atom of the ligand (see Table 1, entries 1, 4, and 8). Additional investigations have shown that modification of the substituents on the sulfonamide group ( $R$ -SO<sub>2</sub>NH-) has only a minor

effect on the stereochemical outcome of the reaction. However, the ligand should preferentially contain an *N*-sulfonyl moiety, as its replacement with an amide (as in **5**, see Table 1, entry 7) or a carbamate resulted in very low to no enantioselectivity.

Most of the ligands discussed above can be readily prepared in enantiomerically enriched form by using previously developed catalytic olefin transformations.<sup>[2]</sup> Furthermore, some hydroxyamino acids are commercially available compounds, and can be easily converted to their corresponding *N*-sulfonyl derivatives.<sup>[11]</sup> For example, *N*-(*p*-toluenesulfonyl)threonine, (2*S*,3*R*)-**6** (see Table 1, entry 8) has been found to be particularly effective for dihydroxylation of cinnamate esters, with 70% *ee* realized in one case (Table 2).<sup>[12]</sup>

Table 2. Asymmetric dihydroxylation of cinnamates using new ligands.

| Olefin    | X               | R           | ee [%] (ligand <b>4</b> ) | ee [%] (ligand <b>6</b> ) |
|-----------|-----------------|-------------|---------------------------|---------------------------|
| <b>7</b>  | H               | Me          | 48                        | 51                        |
| <b>8</b>  | H               | Et          | 50                        | 48                        |
| <b>9</b>  | H               | <i>i</i> Pr | 53                        | 44                        |
| <b>10</b> | NO <sub>2</sub> | Me          | 40                        | 70                        |

In initial studies on the effects of these new second-cycle ligands on the related osmium-catalyzed aminohydroxylation process, we found that both styrene and methyl cinnamate were converted to the corresponding hydroxysulfonamides in high yields with *ee* values ranging from 25 to 55% (Table 3). Very importantly (and in stark contrast to the traditional AA with the cinchona alkaloid derived ligands), no diol formation was detected, and the products were free of osmium contamination.

In summary, a new way of controlling osmium-catalyzed oxidations is offered by a powerful class of ligands, which enforce second-cycle turnover by never leaving the catalytic center. Such processes offer many variables for optimization (in fact, considerably more than the AD offered when it was at the same stage of development) and present an opportunity for a quantum jump in the utility of the osmium-catalyzed oxidation processes. If these second-cycle processes can be optimized, and there are many obvious variables to explore, they should surpass, and thence replace, the existing AD and AA, which as first-cycle processes are dependent on external chiral ligands.

## Experimental Section

Typical dihydroxylation procedure as exemplified for methyl 4-nitrocinnamate: Methyl 4-nitrocinnamate (207 mg, 1 mmol) and *N*-(4-toluenesulfonyl)-L-threonine (13.6 mg, 5 mol %)<sup>[11]</sup> were dissolved in a *t*BuOH/H<sub>2</sub>O mixture (1:1, 6 mL). NMO (50 wt % in water, 228  $\mu$ L, 1.1 mmol) and OsO<sub>4</sub> (0.1 M in acetonitrile, 20  $\mu$ L, 0.002 mmol) were added successively. The pH was adjusted to 5 by addition of 2 N H<sub>2</sub>SO<sub>4</sub> (150  $\mu$ L), and the reaction mixture was stirred vigorously for 24 h, at which time the pH was adjusted

Table 3. Asymmetric aminohydroxylation of olefins using ligands **4** and **6**.<sup>[a]</sup>

| R                  | Ligand (mol %) | Conversion [%] | ratio<br><b>12:13</b> | ee of <b>12</b> [%]<br>(absolute conf.) <sup>[b]</sup> | ee of <b>13</b> [%]<br>(absolute conf.) <sup>[b]</sup> |
|--------------------|----------------|----------------|-----------------------|--------------------------------------------------------|--------------------------------------------------------|
| H                  | <b>4</b> (2)   | 89             | 1:2                   | 45 ( <i>S</i> )                                        | 55 ( <i>R</i> )                                        |
|                    | <b>4</b> (5)   | 86             | 1:2                   | 48 ( <i>S</i> )                                        | 55 ( <i>R</i> )                                        |
|                    | <b>6</b> (2)   | 80             | 1:2                   | 30 ( <i>S</i> )                                        | 25 ( <i>R</i> )                                        |
|                    | <b>6</b> (5)   | 75             | 1:2                   | 47 ( <i>S</i> )                                        | 38 ( <i>R</i> )                                        |
|                    | <b>4</b> (2)   | 85             | 1:2                   | 52 ( <i>2S,3R</i> )                                    | 24 ( <i>2R,3S</i> )                                    |
| COOCH <sub>3</sub> | <b>4</b> (5)   | 93             | 1:2                   | 59 ( <i>2S,3R</i> )                                    | 25 ( <i>2R,3S</i> )                                    |

[a] The reactions were typically run for 20 h and were monitored by HPLC at 228 nm. The regioisomers were separated by reversed-phase preparative liquid chromatography and the *ee* values were determined for each regioisomer separately (R = H, **12**: Chiralcel OG (30% *i*PrOH in hexane), **13**: Chiralpak AS (15% *i*PrOH in hexane); R = COOCH<sub>3</sub>, **12**: Chiralcel OG (30% *i*PrOH in hexane), **13**: Chiralpak AD (20% *i*PrOH in hexane)). [b] The absolute configuration of the products was assigned by comparison with authentic samples.

to **5** again. After an additional 24 h (=98% conversion by liquid chromatography), methyl (2*R,3S*)-(+)-2,3-dihydroxy-3-(*p*-nitrophenyl)-propionate<sup>[13]</sup> was obtained in 70% *ee* (HPLC: Chiralcel OG, 20% *i*PrOH/hexane). The reaction time can be reduced to about 24 h by maintaining constant pH using a pH-stat. A 10 mmol scale reaction, performed under these conditions, afforded product as white solid in 75% yield (1.8 g) and 70% *ee*. Recrystallization from ethanol produced needle-shaped crystals in 57% yield and 81% *ee*.

Typical aminohydroxylation procedure as exemplified for styrene: (2*R,3S*)-*N*-(4-Toluenesulfonyl)-4-nitroisophenylserine (190 mg, 0.5 mmol) and sodium bicarbonate (8.4 mg, 1 mmol) were dissolved in *t*BuOH/H<sub>2</sub>O (1:1, 20 mL). Styrene (1.040 mg, 10 mmol), Chloramine-T trihydrate (2.870 mg, 10 mmol), and K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (36 mg, 0.1 mmol) were then added successively. The reaction mixture was stirred at room temperature for 20 h, at which point HPLC analysis indicated 90% conversion. Sodium sulfite (100 mg) was added, and the mixture was stirred for an additional hour. It was then extracted (ethyl acetate, 3 × 25 mL), dried, and concentrated to yield amorphous solid. Flash chromatography purification afforded a mixture of regioisomers **12:13** (29:71, determined by NMR) as a white crystalline product (2.5 g, 86%). Regioisomers were separated by preparative HPLC (CH<sub>3</sub>CN/H<sub>2</sub>O, 30:70, 0.1% trifluoroacetic acid (TFA), YMC C18 column, 100 mg scale). Enantiomeric excess was determined by chiral HPLC and the absolute configuration was established by comparing optical rotation with authentic samples. (*S*)-**12**, 51%, (Chiralcel-OG, *i*PrOH/hexane, 30:70, 1.5 mL·min<sup>-1</sup>) and (*R*)-**13**, 54% (Chiralcel-AS, *i*PrOH/hexane, 30:70, 1.5 mL·min<sup>-1</sup>).

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## Hydrothermal Synthesis of Molecular Sieve Fibers: Using Microemulsions To Control Crystal Morphology\*\*

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Microporous crystals with pore sizes near molecular dimensions, such as zeolites and molecular sieves, are widely used in shape-selective catalysis and separations, and are being developed for applications in membranes, sensors, and optics.<sup>[1, 2]</sup> Because many emerging applications of microporous materials require precise control of crystal size and orientation,<sup>[3, 4]</sup> there is significant interest in developing new strategies to control crystal structure and morphology. Reverse microemulsions have been used to control the size and shape of some inorganic materials by confining the reaction within surfactant assemblies.<sup>[5, 6]</sup> Microporous zincophosphates have also been crystallized at room temperature from reactants enclosed in reverse microemulsions.<sup>[7, 8]</sup> Zeolites and molecular sieves usually require hydrothermal synthesis conditions ( $T > 100^\circ\text{C}$ ), at which microemulsion formation is difficult to achieve. Here we report the use of reverse microemulsions to control the morphology of crystals of a common aluminophosphate molecular sieve ( $\text{AlPO}_4\text{-5}$ ) during hydrothermal synthesis at  $180^\circ\text{C}$ . Very long fibers are obtained in the microemulsion-based synthesis, a morphology not observed previously for  $\text{AlPO}_4\text{-5}$ . These fibers have linear micropores parallel to the long axis of the fibers. We believe that the high aspect ratio of the fibers should allow their incorporation into materials with controlled crystal orientation. The microemulsion approach could be used to control morphology of other complex materials.

Aluminophosphates are a widely studied class of microporous materials containing a variety of structural types.<sup>[9]</sup> We chose to synthesize aluminophosphate number five ( $\text{AlPO}_4\text{-5}$ ) because of it is one of the most common molecular sieves and has found application in catalysis, nonlinear optics, and membrane separations.<sup>[10]</sup> The crystal structure has the IUPAC name AFI and forms parallel linear pores with uniform diameters of 0.7 nm. The normal route for synthesis of  $\text{AlPO}_4\text{-5}$  begins with a mixture of water, an aluminum source, a phosphorus source, an organic structure-directing agent, and hydrofluoric acid. We conducted phase behavior measurements on several surfactant systems to identify

surfactants capable of solubilizing all of the components of the  $\text{AlPO}_4\text{-5}$  synthesis mixture into a water-in-oil microemulsion. The mixture was treated as a pseudo-ternary system, with oil, "aqueous," and "surfactant" components. Toluene was chosen as the oil phase. The "aqueous" phase was an  $\text{AlPO}_4\text{-5}$  synthesis mixture consisting of water, aluminum triisopropoxide, phosphoric acid, hydrofluoric acid, and triethylamine in a molar ratio of 50:0.8:1.0:0.5:1.2, respectively.<sup>[11]</sup> The "surfactant" phase was a mixture of an ionic surfactant and *n*-butanol. The alcohol was added as a cosurfactant to improve microemulsion formation.<sup>[12]</sup> Three ionic surfactants were investigated; sodium dodecyl sulfate, cetyltrimethylammonium bromide, and cetylpyridinium chloride. Various concentrations of "surfactant" and "aqueous" phases in toluene were examined to determine regimes where an optically transparent, single-phase microemulsion formed at room temperature. It was determined that cetylpyridinium chloride in a 2:1 weight ratio with *n*-butanol had the largest single-phase region, and was capable of solubilizing the greatest amount of the  $\text{AlPO}_4\text{-5}$  synthesis mixture.

The mass fractions of components used for hydrothermal synthesis were 0.219 cetylpyridinium chloride, 0.109 *n*-butanol, 0.492 toluene, and 0.180  $\text{AlPO}_4\text{-5}$  synthesis mixture. The microemulsion was formed by first mixing water, phosphoric acid, and triethylamine together at room temperature for five minutes. Then, cetylpyridinium chloride, *n*-butanol, and toluene were added and the mixture was vigorously shaken for two minutes. At this point, a single-phase microemulsion formed. The microemulsion was aged overnight while stirring at room temperature. Aluminum triisopropoxide was then added and the mixture was shaken vigorously for one minute. After the addition of the aluminum source, the microemulsion was aged at room temperature for two hours. Hydrofluoric acid was then added and the microemulsion was aged for an additional two hours. At room temperature, this mixture forms a transparent single-phase microemulsion, unlike the traditional  $\text{AlPO}_4\text{-5}$  synthesis mixture that appears milky white. Hydrothermal synthesis was conducted by heating the microemulsion to  $180^\circ\text{C}$  in a teflon-lined autoclave for 6 h while stirring. A control was also performed by using the same synthesis conditions, but without toluene, surfactant, and butanol. The solid product was collected by centrifugation, washed with ethanol, and dried overnight in a vacuum oven at  $50^\circ\text{C}$ .

The microemulsion-based synthesis resulted in the formation of long fibers approximately 200–300 nm in width and 15–30 microns in length (Figure 1a), with some groups of fibers aggregated into parallel bundles. The widths of the fibers are very uniform, while the lengths of the fibers vary a great deal. The blunt ends observed on many fibers (Figure 1b), as opposed to sharp points, suggest that these fibers may have been broken during transfer to the scanning electron microscopy stage. By comparison, the traditional synthesis resulted in the formation of irregular hexagonal columns approximately 4–8 microns in width and 5–12 microns in length (Figure 1c). The hexagonal columns appear in a wide variety of sizes. The surfaces of the columns are rough, indicating that they are likely composed of multiply twinned crystals. The powder X-ray diffraction pattern for the material

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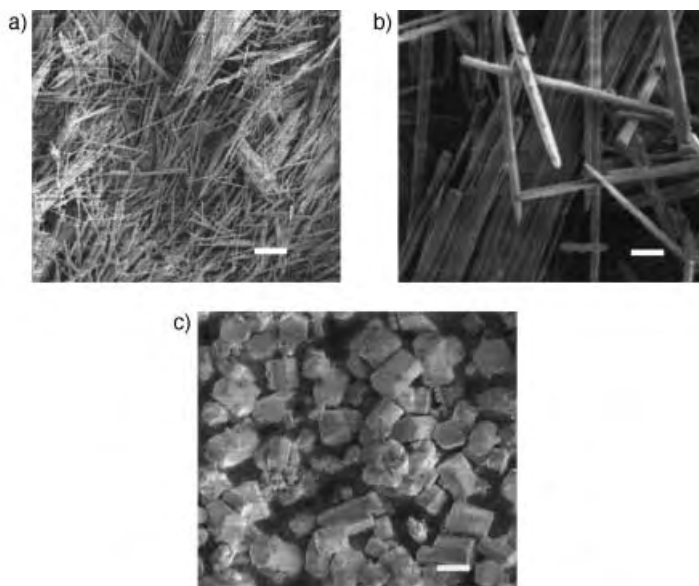


Figure 1. Scanning electron micrographs of  $\text{AlPO}_4\text{-5}$  synthesized in an autoclave at  $180^\circ\text{C}$  for 6 h. a)  $\text{AlPO}_4\text{-5}$  from microemulsion-based synthesis (bar equals 10 microns); b) close-up of fiber ends of  $\text{AlPO}_4\text{-5}$  from microemulsion-based synthesis (bar equals 1 micron); c)  $\text{AlPO}_4\text{-5}$  from traditional synthesis (bar equals 10 microns).

synthesized through the microemulsion-based synthesis is consistent with the AFI structure, and appears similar to the  $\text{AlPO}_4\text{-5}$  diffraction patterns in the literature.<sup>[13]</sup> The one notable difference is the greatly reduced intensity of the (002) peak located at a Bragg angle  $2\theta$  of  $21.3^\circ$ . The loss of intensity of the (002) peak indicates that the fibers are preferentially oriented horizontally, which is consistent with the observed orientation in Figure 1a. From the preferred orientation of the fibers, it can be concluded that the linear micropores are parallel to the long axis of the fibers.

Microwave heating was explored as an alternative route for the synthesis of  $\text{AlPO}_4\text{-5}$  from reactants enclosed in water-in-oil microemulsion droplets. Microwave heating often reduces the crystallization time and/or temperature required for hydrothermal synthesis of zeolites and molecular sieves, including  $\text{AlPO}_4\text{-5}$ .<sup>[14, 15]</sup> Microemulsions were prepared by using the same procedure described above and then heated in a Teflon-lined vessel to  $180^\circ\text{C}$  for 17 min in commercial microwave. Figure 2a shows the scanning electron micrograph of the product formed within the microemulsion after

microwave heating. As with the synthesis in the autoclave, a fibrous product is produced. However, the particle size is much smaller, with widths of approximately 150 nm and lengths of up to 2–3 microns. The smaller fibers also display some tendency to aggregate into parallel bundles. For comparison, Figure 2b shows the product formed from heating the traditional synthesis mixture in the microwave. The product appears as multiply twinned crystals up to 50 microns in length and 10–15 microns in diameter, and is similar to the “barrel-like” morphology described by Wilson in the original synthesis of  $\text{AlPO}_4\text{-5}$ .<sup>[16]</sup> The powder X-ray diffraction patterns for the products from both the traditional synthesis and the microemulsion synthesis confirm the AFI crystal structure (not shown). There is a slight reduction in the intensity of the (002) peak located at a Bragg angle  $2\theta$  of  $21.3^\circ$  for both products, but not as much as observed for the longer fibers synthesized in the autoclave. Apparently, the smaller aspect ratio of the fibers produced in the microwave (10 compared to 100 for the fibers produced in the autoclave) reduces the preferred horizontal orientation.

The formation of microporous materials during hydrothermal synthesis is a complex process of self-assembly coupled with several simultaneous chemical reactions. The mechanism of nucleation and growth is poorly understood, but a recent study has shown that Zeolite A crystals are nucleated within amorphous precursor particles.<sup>[17]</sup> The size and shape of the final crystal was the same as the amorphous precursor particle, but further crystal growth could be attained upon heating through Ostwald-ripening type mechanism. It has been proposed that  $\text{AlPO}_4\text{-5}$  crystallization occurs through a similar route where an amorphous precursor consisting of a self-assembled array of inorganic and organic (structure-directing agent) material converts to  $\text{AlPO}_4\text{-5}$  crystals upon heating.<sup>[14]</sup> Concentrated water-in-oil microemulsions often form cylindrical aggregates, and these aggregates have been used as templates to form rod-shaped materials.<sup>[18]</sup> We believe that a similar templating mechanism may be operative in the molecular sieve synthesis. Such a mechanism would involve “dual” templating: the structure-directing agent templates the micropores within the crystal, while the surfactant aggregate surrounding the amorphous precursor templates the crystal size and shape. While we believe the surfactant aggregates template crystal nucleation, the final crystal size is much larger than typical surfactant aggregates, so crystal growth must continue outside the microemulsion droplets. The microporous  $\text{AlPO}_4\text{-5}$  fibers synthesized in the microemulsion may find application in optics, sensors, or membranes, where the high aspect ratio of the fibers will allow deposition onto substrates with controlled crystal orientation.

### Experimental Section

**Phase behavior measurements:** An  $\text{AlPO}_4\text{-5}$  synthesis mixture consisting of water, aluminum triisopropoxide, phosphoric acid, hydrofluoric acid, and triethylamine in a molar ratio of 50:0.8:1.0:0.5:1.2, respectively, was formed and aged for at least 4 h at room temperature. In a second container, surfactant, butanol, and toluene were added in concentrations of 60 wt % toluene and 40 wt % surfactant + butanol. The  $\text{AlPO}_4\text{-5}$  synthesis mixture was added in 50  $\mu\text{L}$  increments to 5 g of the surfactant, toluene, and butanol

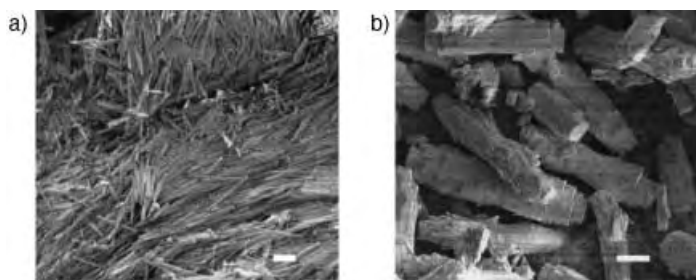


Figure 2. Scanning electron micrographs of  $\text{AlPO}_4\text{-5}$  synthesized by microwave heating at  $180^\circ\text{C}$  for 17 min. a)  $\text{AlPO}_4\text{-5}$  from microemulsion-based synthesis (bar equals 1 micron); b)  $\text{AlPO}_4\text{-5}$  from traditional synthesis (bar equals 10 microns).

mixture. After each addition of the  $\text{AlPO}_4\text{-5}$  synthesis mixture, the container was stirred for several minutes before making visual observations. The minimum amount of  $\text{AlPO}_4\text{-5}$  synthesis mixture required to form the microemulsion was determined by the observation of a transparent single-phase. The maximum solubility of  $\text{AlPO}_4\text{-5}$  synthesis mixture in the microemulsion was defined by the onset of visual turbidity. The ratio of butanol to surfactant was varied from 2:1 to 1:2. The single-phase microemulsion did not form in the absence of butanol.

**Hydrothermal synthesis:** Autoclave synthesis was conducted in a teflon-lined pressure vessel (Parr, model 4744) wrapped in heating tape and controlled to a temperature of 180 °C for 6 h. The reactor contents were stirred continuously using a magnetically coupled teflon stir bar. Microwave synthesis was conducted in teflon acid digestion vessels in a CEM MDS-2000 oven. The vessels were heated to 180 °C for 17 min without stirring.

Powder X-ray diffraction spectra were collected by using a Scintag XDS2000 diffractometer using an accelerating voltage of 45 kV and intensity of 40 mA. The diffraction pattern was collected from an angle  $2\theta$  of 5 to 50°, using a step size of 0.02° and a collection time at each step of 3 s. Scanning electron micrographs were obtained by using a JEOL 6300FX high-resolution scanning electron microscope operating at an accelerating voltage of 1.0 kV.

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## Biomimetic $\text{NAD}^+$ Models for Tandem Cofactor Regeneration, Horse Liver Alcohol Dehydrogenase Recognition of 1,4-NADH Derivatives, and Chiral Synthesis\*\*

H. Christine Lo and Richard H. Fish\*

In memory of Dr. E. Steckhan

The biocatalysis discipline has the potential to generate important chiral organic compounds, by the use of enzymes, usually in the presence of critical cofactors.<sup>[1,2]</sup> Therefore, practical methods for the regeneration of the coenzyme 1,4-NADH are significant in biocatalysis.<sup>[3–5]</sup> In this manner, a variety of transition metal hydrides have been evaluated as catalysts for the regioselective reduction of  $\text{NAD}^+$  and  $\text{NAD}^+$  models to the corresponding 1,4-NADH derivatives to develop faster rates and a more economical regeneration process.<sup>[6–9]</sup> In the most significant example, Steckhan et al. described the in situ generation of  $[\text{Cp}^*\text{Rh}(\text{bpy})(\text{H})]^+$  ( $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$ ,  $\text{bpy} = 2,2'$ -bipyridyl) for the regiospecific reduction of natural  $\text{NAD}^+$  to 1,4-NADH,<sup>[7]</sup> and then demonstrated the cofactor regeneration process in enzymatic chiral reduction reactions with horse liver alcohol dehydrogenase (HLDAH).<sup>[10–12]</sup>

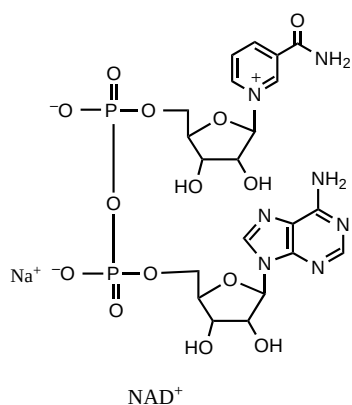
More importantly, we recently reported the source of this unusually high regioselectivity for 1,4-NADH and other mechanistic aspects with a model  $\text{NAD}^+$  compound, 1-benzylnicotinamide triflate (**1**; Scheme 1). The reaction in  $\text{H}_2\text{O}/\text{THF}$  (1:1) used  $[\text{Cp}^*\text{Rh}(\text{bpy})(\text{H}_2\text{O})](\text{OTf})_2$  (**2**) as the catalyst precursor, and sodium formate as the hydride source to provide exclusively the kinetic product, 1-benzyl-1,4-dihydronicotinamide (**3**).<sup>[13]</sup>

Furthermore, we also recently used an aqueous  $\text{NAD}^+$  model,  $\beta$ -nicotinamide-5'-ribose methyl phosphate (**4**) and demonstrated its similar regioselective reduction with  $[\text{Cp}^*\text{Rh}(\text{bpy})(\text{H})]^+$ , formed in situ, to give the corresponding 1,4-dihydronicotinamide-5'-ribose methyl phosphate (**5**) at pH 6.5.<sup>[14]</sup>  $\text{NAD}^+$  model **4** bears a structural resemblance to  $\text{NAD}^+$  (a monoribose phosphate moiety, but with no pyrophosphate or adenosine substituents), while  $\text{NAD}^+$  biomimetic **1** has a simple 1-benzyl group instead of the ribose, pyrophosphate, and adenosine groups.

The initial rates ( $r_i$ ) of the regioselective reduction of both **1** in  $\text{H}_2\text{O}/\text{THF}$  (4:1) and **4** in  $\text{H}_2\text{O}$  at pH 6.5 with  $[\text{Cp}^*\text{Rh}(\text{bpy})(\text{H})]^+$  (generated in situ) to give their corre-

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sponding 1,4-dihydro analogues (**3** and **5**) were comparable to that of NAD<sup>+</sup> in H<sub>2</sub>O at pH 6.5 (Scheme 1; turnover frequency (TOF): 20 h<sup>-1</sup>).<sup>[14]</sup> Therefore, we decided to use both **1** and **4** as biomimetics of NAD<sup>+</sup> in chiral reduction reactions, in conjunction with the above-mentioned cofactor regeneration method.<sup>[13, 14]</sup> Moreover, recent studies with other NAD<sup>+</sup> biomimetics by Lowe and co-workers showed that primary alcohols were oxidized to aldehydes and that 1,4-NADH biomimetic was produced. The reverse reaction, that is, the reduction of aldehydes to alcohols, along with NAD<sup>+</sup> biomimetic production, was not observed.<sup>[15–17]</sup>

Two questions arose: What is the role of each substituent on the 1,4-dihydronicotinamide nucleus, including ribose, pyrophosphate, and adenosine groups? Will HLADH enzyme recognition at the binding site for the cofactor prevail to provide chiral reduction products with the most important structural feature still present in our biomimetic 1,4-NADH models: the 1,4-dihydronicotinamide nucleus?<sup>[18–21]</sup>

The preliminary tandem cofactor regeneration and chiral synthesis experiments with substrates **6–10** (Table 1) and NAD<sup>+</sup> biomimetics **1** and **4**, with NAD<sup>+</sup> as a comparison, provided quite startling and dramatic results. For example, in

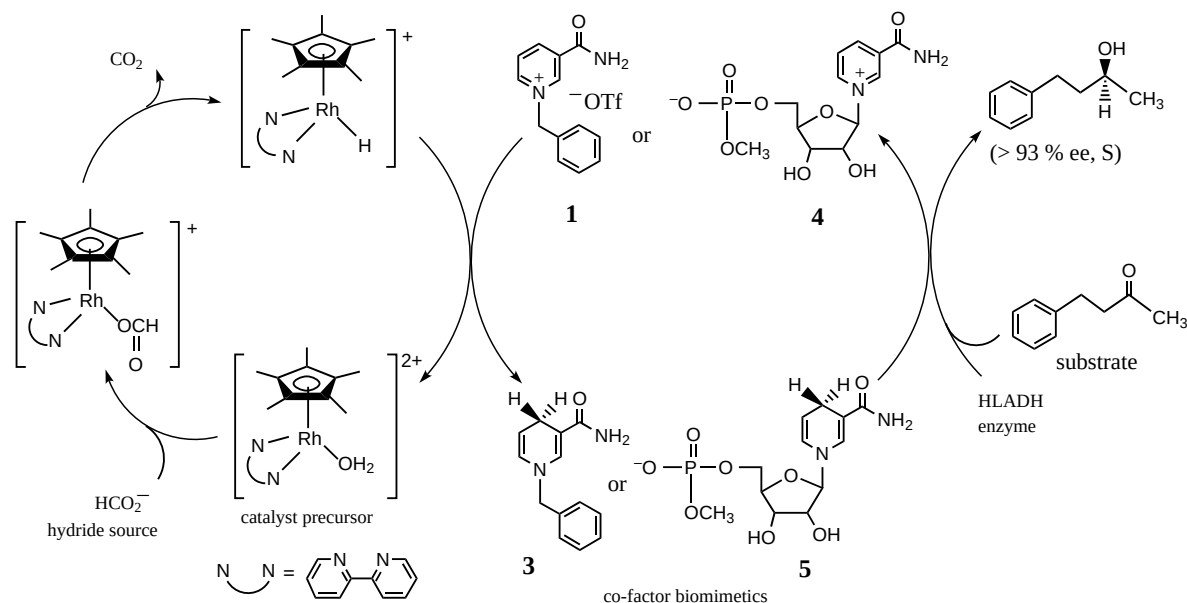
Table 1. Enzymatic reductions of prochiral ketones with NAD<sup>+</sup> models **1** and **4**: turnover frequencies and *ee* values.<sup>[a,b]</sup>

| substrate                                                                        | product                                                                            | % yield | TOF [d <sup>-1</sup> ] | <i>ee</i> [%, S]      |
|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------|------------------------|-----------------------|
| PhCH <sub>2</sub> CH <sub>2</sub> C(=O)CH <sub>3</sub><br><b>6</b>               | PhCH <sub>2</sub> CH <sub>2</sub> CH(OH)CH <sub>3</sub><br><b>11</b>               | 90(91)  | 30(31)                 | 93(93)                |
| PhCH <sub>2</sub> C(=O)CH <sub>3</sub><br><b>7</b>                               | PhCH <sub>2</sub> CH(OH)CH <sub>3</sub><br><b>12</b>                               | 55(59)  | 18(19)                 | > 99(99)              |
| PhC(=O)CH <sub>3</sub><br><b>8</b>                                               | PhCH(OH)CH <sub>3</sub><br><b>13</b>                                               | 5(5)    | 4(4)                   | > 96(96)              |
| CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> C(=O)CH <sub>3</sub><br><b>9</b> | CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH(OH)CH <sub>3</sub><br><b>14</b> | 41(59)  | 14(20)                 | 85(85) <sup>[c]</sup> |

[a] Models **1** and **4** provided similar results within experimental error (< 2 %). The results obtained with NAD<sup>+</sup> are given in parenthesis. [b] The *ee* values were determined by means of GC analysis with a modified  $\beta$ -cyclodextrin capillary column. [c] Based on the analysis of carbamate diastereomers with an optically pure isocyanate derivative.

the presence of HLADH, **6** was reduced to give (*S*)-**11** (> 93 % *ee*; TOF ~ 30 d<sup>-1</sup>). Both NAD<sup>+</sup> models **1** and **4** gave results similar to those with NAD<sup>+</sup> (Table 1). Clearly, all that is necessary for HLADH recognition of the 1,4-NADH biomimetics **3** and **5** is the 1,4-dihydronicotinamide moiety. The possible binding role of 1-benzyl and of ribose-5'-methyl phosphate in the hydrophobic pocket of HLADH does not appear to compromise the transfer of hydride to the ketone substrate to provide chiral alcohol (Scheme 1).

A structure–reactivity study of a variety of ketone substrates (Table 1) further showed that benzyl methyl ketone (**7**) gave (*S*)-**12** (> 99 % *ee*, TOF 18 d<sup>-1</sup>), whereas benzophenone (**8**) was extremely slow (TOF, 2 d<sup>-1</sup>) in providing chiral (*S*)-**13** (> 93 % *ee*) after 24 h. Alkyl ketone **9** provided predominantly (*S*)-**14** (85 % *ee*), similar to the results



Scheme 1. Plausible catalytic reduction cycle for the synthesis of 1,4-NADH biomimetics, **3** or **5**, followed by a catalytic cycle for chiral alcohol synthesis from ketone substrates with the enzyme, HLADH.

obtained with NAD<sup>+</sup>. This may demonstrate that the binding site for this type of alkyl ketone is not as rigid as the binding site for phenethyl ketone to engender higher chirality to the alcohol product.

Alternatively, the enantiomers of bulky norcamphor (**10**) were reduced at different rates and also provided a different diastereomeric mixture of predominantly *endo* chiral alcohols. As shown in Table 2, one enantiomer of **10** gave an approximately equal mixture of the *exo* and *endo* alcohols, whereas the other gave exclusively the *endo* alcohol with no *exo* alcohol detected.

Table 2. Enzymatic conversion of racemic norcamphor: turnover frequency (TOF) and yield with NAD<sup>+</sup> models **1** and **4**.<sup>[a]</sup>

| Substrate                                             | Product                                                             | Yield [%]   | TOF [d <sup>-1</sup> ] |
|-------------------------------------------------------|---------------------------------------------------------------------|-------------|------------------------|
|                                                       |                                                                     | 86 (94)     | 28 (29)                |
| (+)-(1 <i>S</i> ,4 <i>R</i> )- <b>10</b><br>0.5 equiv | (+)-(1 <i>S</i> ,2 <i>R</i> ,4 <i>R</i> )- <b>10</b><br>0.45 (0.48) | 0.0 (0.0)   |                        |
|                                                       |                                                                     |             |                        |
| (-)-(1 <i>R</i> ,4 <i>S</i> )- <b>10</b><br>0.5 equiv | (-)-(1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i> )- <b>10</b><br>0.21 (0.25) | 0.20 (0.21) |                        |

[a] The results obtained with NAD<sup>+</sup> are given in parenthesis.

Interestingly, the hydride transfer pathway from 1,4-NADH to the HLADH-bound ketone is still very controversial; various mechanisms have been proposed, but none appear very satisfactory.<sup>[22]</sup> The previously formulated results indicated that the initial binding process of natural 1,4-NADH occurs in proximity to the Zn<sup>2+</sup> center of HLADH, and the Zn<sup>2+</sup>-bound substrate.<sup>[23, 24]</sup> In a manner similar to that of the [Cp\*Rh(bpy)H]<sup>+</sup> binding of biomimetic **1** for the regioselective production of **3**,<sup>[13, 14]</sup> we also envision the possibility that the carbonyl function of the amide group of 1,4-NADH, and that of biomimetics **3** or **5**, might weakly bind to the Zn<sup>2+</sup> center to stabilize this hydride-transfer process (Scheme 2).

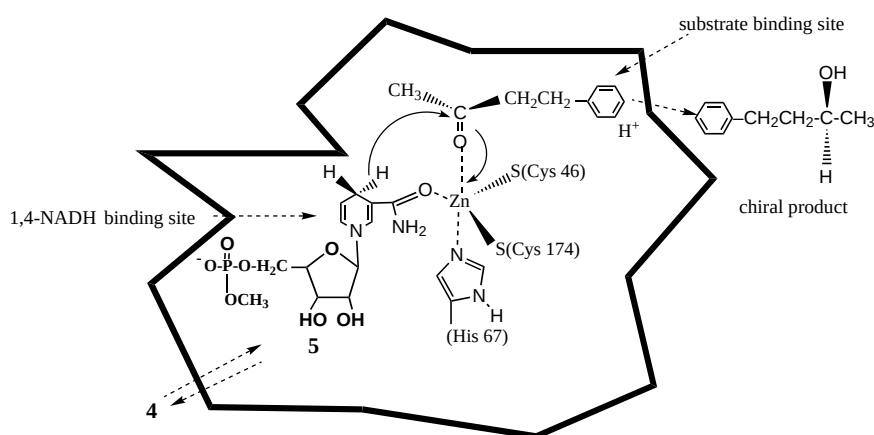
This possible Zn<sup>2+</sup>-binding process of the cofactor during the transfer of hydride from **5** to the *Re* face of the carbonyl group could also conceivably add stability to the microscopic reverse reaction, that is, hydride transfer from a specific C–H of RCH<sub>2</sub>OZn to **4**, to give a C=O product and **5**. We have, in fact, shown that the reverse reaction, (*S*)-**14** to **9** occurs with NAD<sup>+</sup> biomimetic **4**, whereas the *R* enantiomer was found to be extremely slow.

This potential binding regime allows the Zn<sup>2+</sup> metal center to become 4- or 5-coordinate during the 1,4-NADH hydride-transfer process in the presence of the carbonyl substrate. Recently, Sagi and co-workers<sup>[25]</sup> have strengthened the concept of the Zn<sup>2+</sup> center being a template for much of the ADH reactivity. They demonstrated with a thermophilic ADH enzyme (TbADH) that the Zn<sup>2+</sup> center exhibits a pentacoordinate structure, and developed an active-site model that reflected their results with Asp 150, His 59, Glu 60, Cys 37, and DMSO as the surrogate substrate, coordinated to the Zn<sup>2+</sup>.<sup>[25]</sup>

In conclusion, we have demonstrated that biomimetic NAD<sup>+</sup> models, which were structurally modified to retain the nicotinamide nucleus as NAD<sup>+</sup> and either one similar substituent, the ribose-5'-phosphate group, or none, the 1-benzyl group, can be converted regioselectively into their 1,4-dihydronicotinamide analogues. We have clearly shown for the first time, to the best of our knowledge, that these 1,4-NADH biomimetics are recognized by the HLADH cofactor binding site in the chiral synthesis of aryl/alkyl-substituted alcohols. Although the economic benefits of this discovery can not be fully evaluated at this time for biocatalytic applications, it is clear from the presented results, and previous observations,<sup>[15–17]</sup> that some structural features of 1,4-NADH need not be present for enzyme recognition and for the synthesis of chiral organic compounds. We hope that our results pave the way for the possible utilization of NAD<sup>+</sup> models such as **1** and **4** in a variety of biocatalytic processes of industrial importance; model **1** and other potential analogues are more stable under conditions that might cause the NAD<sup>+</sup> to be hydrolytically compromised.<sup>[26, 27]</sup>

## Experimental Section

**General Procedure (Reduction):** [Cp\*Rh(bpy)-(H<sub>2</sub>O)]OTf<sub>2</sub> (1.9 mg, 2.61 × 10<sup>-3</sup> mmol), sodium formate (17.8 mg, 261.69 × 10<sup>-3</sup> mmol), NAD<sup>+</sup> (or NAD<sup>+</sup> models **1** or **4**) (8.1 mg, 11.23 × 10<sup>-3</sup> mmol), and HLADH (10 units) were placed in a 10-mL Schlenk flask, and Schlenk techniques were used to deoxygenate the solid mixture. Under positive argon pressure, potassium phosphate buffer (5 mL, 100 mM, pH 7.02, deoxygenated) and the carbonyl substrate (83.58 × 10<sup>-3</sup> mmol, deoxygenated) were added successively through a syringe. The reaction flask was immediately capped securely with a glass stopper and shaken by using a shaker in a 30 °C water bath. The reaction was monitored by means of GC, equipped with a β-cyclodextrin column (Supelco, β-DEX-225). The products were identified by comparing the retention time with authentic chiral samples, and were confirmed by GC-MS. The *ee* values of the products were directly determined by calculating their relative areas from the chromatograms. The progress of the reaction was obtained by mixing the reaction



Scheme 2. Postulated active-site model for HLADH with 1,4-NADH biomimetic **5** as hydride source and phenethyl methyl ketone (**6**) as substrate.

aliquot with an internal standard (cyclohexanol in phosphate buffer), and then calibrating the measured relative area in the chromatogram with their corresponding response factors. The reaction was monitored for 24 h.

**Control Experiments:** No chiral alcohol product was formed in the absence of the HLADH enzyme, while no ketone was reduced to alcohol in the presence of the model cofactors **1** and **4**. The latter result shows that **1** and **4** preferentially bind to the Cp\*Rh center in the presence of the ketone, and they are reduced regioselectively to their 1,4-NADH derivatives **3** and **5**, all in the absence of HLADH.

**General Procedure (Oxidation):** NAD<sup>+</sup> ( $83.58 \times 10^{-3}$  mmol) or NAD<sup>+</sup> models **1** or **4** and HLADH (10 units) were placed in a 10-mL Schlenk flask, and Schlenk techniques were used to deoxygenate the solid mixture. Under positive argon pressure, potassium phosphate buffer (5 mL, 100 mM, pH 7.04, deoxygenated) and (S)-2-pentanol ( $83.58 \times 10^{-3}$  mmol) were added successively through a syringe. The reaction flask was immediately capped securely with a glass stopper and shaken by using a shaker at room temperature. The progress of the reaction was monitored by means of GC, and the product, 2-pentanone, was identified by comparing the retention time with that of an authentic sample. The oxidation of (R)-2-pentanol was also tested under the same conditions, and its reaction rate was found to be much slower than that of (S)-2-pentanol. The relative rates of (S)- and (R)-2-pentanol in the first 24 hr were ~4:1. Additionally, the reactions were found to reach equilibrium after ~60 h (in the case of (S)-2-pentanol), at which point both 2-pentanol and 2-pentanone were present in the reaction mixture in a ratio of ~40:60. The same procedure described in the example with NAD<sup>+</sup> was followed with the water soluble model **4**. Both racemic 2-pentanol and (S)-2-pentanol were tested, and similar results were obtained as stated in the case of NAD<sup>+</sup>, except that the reaction rate became slower after 24 h.

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## Transfer of Chiral Information through Achiral Ion Recognition by a Novel Pseudocrown Ether with a Binaphthyl Moiety

Tatsuya Nabeshima,\* Akihiro Hashiguchi, Toshiyuki Saiki, and Shigehisa Akine

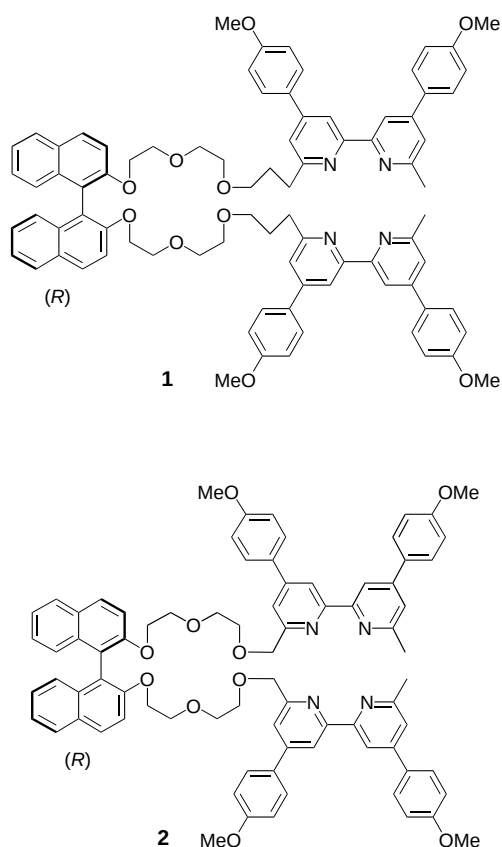
Chiral products obtained from metabolic processes are often used as reactants for subsequent asymmetric reactions in different chiral environments.<sup>[1]</sup> Not only chemical reactions but also physical events, such as the selective transport of chiral substrates, require chiral communication between the molecules engaged in the chiral process. Thus, transfer, transduction, modulation, and amplification of chiral information are essential issues for all chiral phenomena. These processes, however, are usually regulated by chiral molecules. Hence, the regulation of such chiral events by an achiral species is extremely fascinating and important.

Allostery and feedback are good examples of the transfer of molecular information, and they regulate many biological events that are linked to each other.<sup>[2]</sup> These regulating processes play an important role in controlling the function of proteins and they are effective for triggering a certain cascade of reactions in which molecular information is transferred and/or amplified. Many artificial allosteric receptors have recently been reported in which their function is regulated by a single effector, although multistep response to several different stimuli should be very useful for constructing cascade systems<sup>[3]</sup> and molecular logic devices.<sup>[4, 5]</sup>

Here we report that podand **1**<sup>[6]</sup> dually responds to external stimuli, its conversion to a pseudocrown ether complex [Cu<sup>I</sup>(**1**)], and the transfer of chiral information in [Cu<sup>I</sup>(**1**)] by achiral guests, namely alkali metal ions. Precursor

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**1** for the pseudocrown ether complex possesses two polyether chains that connect the (R)-1,1'-binaphthyl and 2,2'-bipyridine moieties. If 1:1 complexation of **1** with a Cu<sup>I</sup> ion occurs, the desired host [Cu<sup>I</sup>(**1**)] with a cyclic binding site for an alkali metal ion is produced. There are two diastereomers of [Cu<sup>I</sup>(**1**)], that is, a helical and nonhelical structure.

Quantitative formation of the red [Cu<sup>I</sup>(**1**)] complex was ascertained by UV/Vis and <sup>1</sup>H NMR spectroscopies.<sup>[6, 7]</sup> A metal-to-ligand charge-transfer (MLCT) absorption characteristic of a tetrahedral Cu<sup>I</sup>–bipyridine complex<sup>[7]</sup> appeared at 480 nm upon addition of Cu<sup>I</sup> ions. The isotope distribution observed in the electrospray ionization (ESI) mass spectrum for [Cu<sup>I</sup>(**1**)] is in good agreement with the theoretical pattern. This geometry is also supported by new signals for the methyl protons adjacent to the bipyridine moieties appearing upfield in the <sup>1</sup>H NMR spectrum.<sup>[7b,c]</sup> UV/Vis (1,2-dichloroethane:CH<sub>3</sub>CN 50:1) and <sup>1</sup>H NMR (CDCl<sub>3</sub>:CD<sub>3</sub>CN:CD<sub>3</sub>OD 47:3:50) titrations indicate the quick formation of a stable complex between **1** and a Cu<sup>I</sup> ion. There are two signals in the <sup>1</sup>H NMR spectrum arising from the picolyl methyl protons which can be assigned to the two diastereomers. Consequently, the ratios of the diastereomers can be calculated to be 42:58<sup>[8]</sup> and 43:57 for [Cu<sup>I</sup>(**1**)] and [Cu<sup>I</sup>(**2**)], respectively.

Significant changes in the <sup>1</sup>H NMR spectrum of [Cu<sup>I</sup>(**1**)] (Figure 1) were observed on addition of NaTFPB (TFPB<sup>−</sup>: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). In particular, the chemical shifts of the resonances attributed to the polyether chains changed drastically, which indicates that the Na<sup>+</sup> ion complexes inside the cavity of the pseudocrown ether of [Cu<sup>I</sup>(**1**)]. Analysis of the resulting complex by ESI-

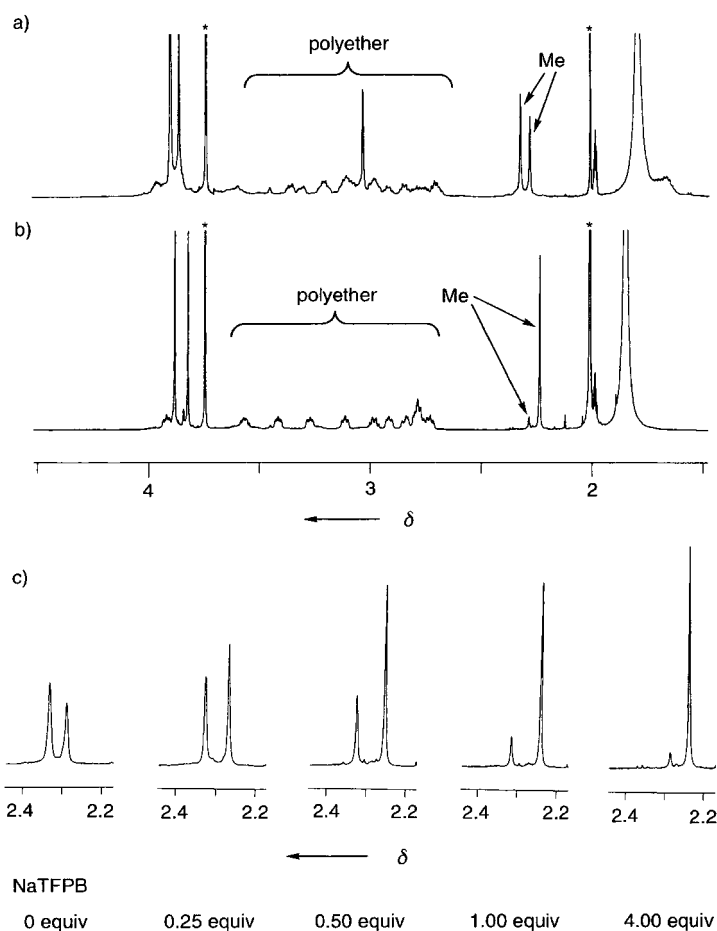


Figure 1. <sup>1</sup>H NMR spectra of [Cu<sup>I</sup>(**1**)] in a mixture of CDCl<sub>3</sub> and CD<sub>3</sub>CN (95:5): a) [Cu<sup>I</sup>(**1**)]TFPB; b) [Cu<sup>I</sup>(**1**)]TFPB and four equivalents of NaTFPB; c) The signals for the picolyl methyl groups in the absence and presence of NaTFPB (0.25–4 equiv). \* denotes solvent signals.

MS also suggests the formation of the ternary complex of **1**, Cu<sup>I</sup>, and Na<sup>+</sup>. In a more polar solvent (CDCl<sub>3</sub>:CD<sub>3</sub>OD 4:1), however, an excess amount (2 equiv) of Na<sup>+</sup> ions resulted in no significant changes in the <sup>1</sup>H NMR spectrum. The addition of *n*Bu<sub>4</sub>NTPFB had no effect on the spectra. This result is explained by the *n*Bu<sub>4</sub>NTPFB ion being too large to coordinate with [Cu<sup>I</sup>(**1**)], as judged by the inspection of a CPK model. In contrast to [Cu<sup>I</sup>(**1**)], the addition of Na<sup>+</sup> and K<sup>+</sup> ions caused no spectral changes to [Cu<sup>I</sup>(**2**)], thus showing that the complex had practically no affinity for Na<sup>+</sup> and K<sup>+</sup> ions. This remarkable selectivity of [Cu<sup>I</sup>(**1**)] and its respective affinity, relative to [Cu<sup>I</sup>(**2**)], probably results from the smaller electrostatic repulsion between the Na<sup>+</sup> and Cu<sup>I</sup> ions and/or from the higher flexibility of the polyether chains as a consequence of the longer trimethylene spacers between the polyether chain and the bipyridine units. The ratio of the two signals for the picolyl methyl protons in the <sup>1</sup>H NMR spectrum of [Cu<sup>I</sup>(**1**)] increased considerably in proportion to the amount of Na<sup>+</sup> added. One diastereomer was formed slightly more favorably (42:58) in the absence of Na<sup>+</sup> ions. However, the distribution of the diastereomers was reversed in the presence of excess Na<sup>+</sup> ions (4 equiv), and the other isomer formed predominately (89:11). It is noteworthy that the ratio is independent of the concentration (1.0–8.0 mM) of

[Cu<sup>I</sup>(**1**)]. This fact again indicates that the two signals do not come from *n:n* oligomeric products but from the two 1:1 isomers. Thus, the increase in the ratio reflects the higher affinity of one diastereomer toward Na<sup>+</sup> ions than that of the other. The changes in the ratio and chemical shifts of the signals for the methyl protons were analyzed by nonlinear regression to give the association constants ( $K_a$ ) between [Cu<sup>I</sup>(**1**)] and Na<sup>+</sup>. The  $K_a$  value of one diastereomer is 15 times larger than that of the other. The effective coordination of the polyether moieties in [Cu<sup>I</sup>(**1**)] to an Na<sup>+</sup> ion induced a conformational change, and thus a shift in the equilibrium between the diastereomers. The enhancement of the diastereomeric excess (77%, 4 equiv of Na<sup>+</sup>) in [Cu<sup>I</sup>(**1**)] clearly shows that the chirality of the (*R*)-1,1'-binaphthyl moiety is transferred to the tetrahedral Cu<sup>I</sup>-bipyridine complex by complexation with an Na<sup>+</sup> ion, which acts not only as an achiral guest but also as a mediator of chiral information. It is notable that the addition of [18]crown-6 to a mixture of **1**, Cu<sup>I</sup>, and Na<sup>+</sup> (1:1:2) decreased the diastereomeric ratio to the original value obtained in the absence of Na<sup>+</sup> ions. This effect is attributed to the removal of the Na<sup>+</sup> ion from the cavity of the pseudocrown ether. The addition of K<sup>+</sup> ions (4 equiv) has a smaller effect on the ratio of diastereoisomers (85:15), and the ratio was even smaller with Cs<sup>+</sup> ions (66:34). The dependency of the ratio on the size of the alkali metal ions suggests there is a dipole-ion interaction between the guests and the pseudocrown ring.

Preferential formation of one diastereomer of [Cu<sup>I</sup>(**1**)] was also shown by CD spectroscopy (Figure 2). The complex [Cu<sup>I</sup>(**1**)] itself exhibited very weak Cotton effects (almost CD silent) in the region of the MLCT band. However, positive

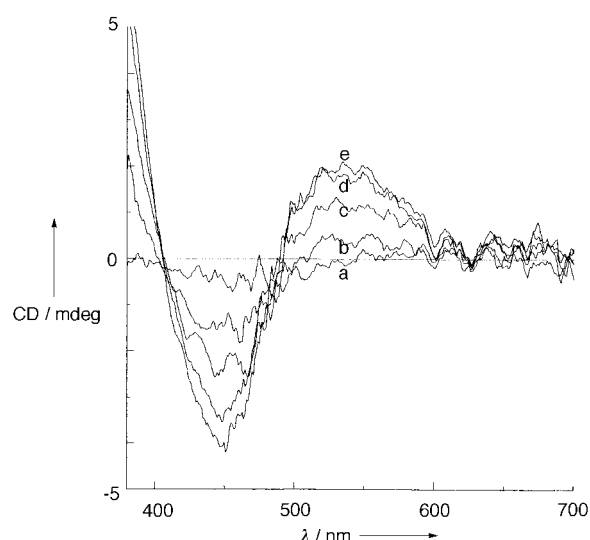
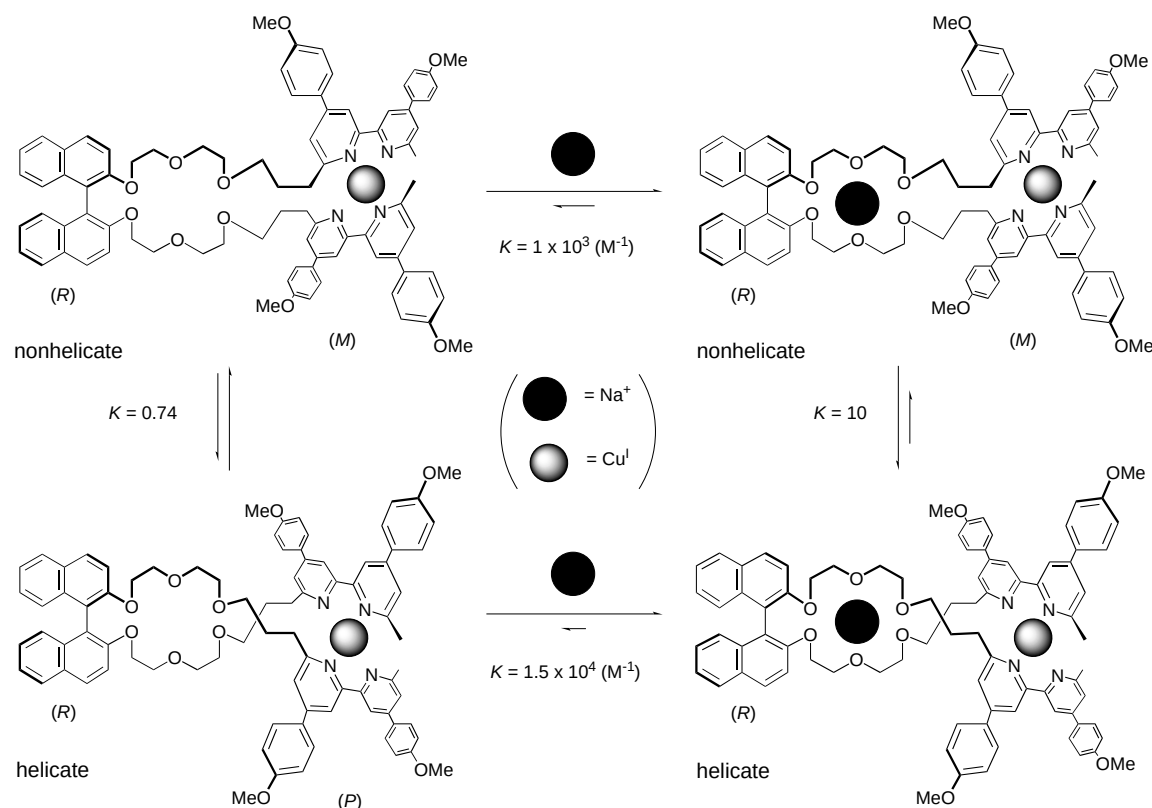


Figure 2. CD Spectral Changes of [Cu<sup>I</sup>(**1**)]TFPB by the addition of NaTFPB in a mixture of CH<sub>2</sub>ClCH<sub>2</sub>Cl and CH<sub>3</sub>CN (95:5) at 25 °C. Concentration of [Cu<sup>I</sup>(**1**)]TFPB = 2.0 mM. a) NaTFPB: 0 equiv; b) NaTFPB: 0.25 equiv; c) NaTFPB: 0.50 equiv; d) NaTFPB: 1.0 equiv; e) NaTFPB: 2.0 equiv.

and negative Cotton effects were distinctly observed in the presence of Na<sup>+</sup> ions, which is consistent with the predominant formation of the right-handed, (that is, helical) structure.<sup>[9]</sup> The formation of a 1:1 complex between [Cu<sup>I</sup>(**1**)] and Na<sup>+</sup> was evident from monitoring the increase in the CD intensity.<sup>[10]</sup> <sup>1</sup>H NMR spectroscopic studies have shown that the helical diastereomer of the pseudocrown ether binds Na<sup>+</sup> ions even more strongly than the other (Scheme 1). Inspection



Scheme 1. Transfer of chiral information from the binaphthyl moiety to the [Cu<sup>I</sup>(bpy)<sub>2</sub>] complex of **1**. bpy = 2,2'-bipyridine.



of CPK models suggested that the helical structure is more compact and rigid, and that the helicate provides a more favorable binding site for Na<sup>+</sup> ions than the nonhelicate. Finally, the observation of a modulation of the CD intensity in the MLCT region indicates that this system works as an AND device for CD output by utilizing coordination and chiral information: The Cu<sup>I</sup> and Na<sup>+</sup> ions act as the input signals<sup>[4, 5]</sup> and there is only a CD response if the system receives both input signals.

All the spectral data obtained indicate unambiguously that there is an efficient and intramolecular transfer of chiral information from the binaphthyl moiety to the [Cu<sup>I</sup>-bipyridine] complex through the coordination of an achiral Na<sup>+</sup> ion. This complexation makes the pseudocrown ring more rigid than in the Na<sup>+</sup>-free [Cu<sup>I</sup>(1)] complex. This rigidity results in a significant reduction in the loss of chiral information from the binaphthyl unit to the Cu<sup>I</sup> complex through the polyether spacers and results in effective chiral communication being achieved.

Helicates such as the [Cu<sup>I</sup>(1)] complex are also considered to be strong candidates for intermolecular chirality transfer since helical metal complexes have a high potential for chiral recognition and interaction with helical biomolecules such as DNA<sup>[11]</sup> and proteins with an  $\alpha$ -helical structure. A preliminary experiment showed that [Cu<sup>I</sup>(1)] bound to amino acid derivatives, thus an interaction with proteins can be expected. We are currently investigating chiral information transfer systems by using an achiral mediator for chirality.

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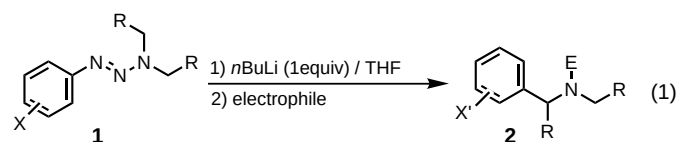
## $\alpha$ -Lithiation of 1-Aryl-3,3-dialkyltriazenes and Intramolecular Conversion to Benzylamine and Tetrahydrobenzotriazine Derivatives\*\*

Keiji Nishiwaki,\* Takashi Ogawa, and Keizo Matsuo\*

1-Aryl-3,3-dialkyltriazenes are utilized in many ways in organic syntheses, for example, as protective groups for aniline derivatives,<sup>[1]</sup> as precursors of benzyne,<sup>[2]</sup> as well as in diazo coupling,<sup>[3]</sup> Sandmeyer–Gattermann reactions,<sup>[4]</sup> and hydroxylation of positive ion exchange resins.<sup>[5]</sup> Recently, Nicolaou et al. showed that aryltriazenes can be used in the construction of aryl ethers, and applied this method to the synthesis of vancomycin.<sup>[6]</sup> In combinatorial chemistry, triazenes were used as linkers in solid-phase synthesis<sup>[7]</sup> and as alkylating polymers in solution-phase synthesis.<sup>[8]</sup> Haley et al. reported thermal cyclization of triazenes.<sup>[9]</sup>

Here we report on the transformation of 1-aryl-3,3-dialkyltriazenes into benzylamines and dearomatized compounds, which involves a novel intramolecular carbon–carbon bond-forming reaction in which a lithiated alkyl group on the nitrogen atom in the 3-position<sup>[10]</sup> attacks the aromatic ring as a nucleophile.

The triazenes were prepared in good yields from the corresponding primary aromatic amines by standard methods (NaNO<sub>2</sub>/HCl, then addition of the respective amine). The general procedure for the transformation of the triazenes into benzylamines is as follows. The triazenes were treated with *n*BuLi (1 equiv) in THF at 0°C for 1 h, followed by the addition of electrophiles to produce the corresponding benzylamine derivatives [Eq. (1)]. The results are summar-



ized in Table 1. The addition of Boc<sub>2</sub>O instead of H<sub>2</sub>O as an electrophile greatly increased the yield (entries 1 and 3). When *o*- and *p*-methylphenyltriazenes were treated as above, *m*-methylbenzylamine was formed in both cases, but the yield of the product was superior in the latter case (entries 6–8). Some *p*-substituted triazenes were transformed into *m*-substituted benzylamine derivatives (entries 9–12). In the case of the *m*-substituted triazenes, mixtures of *o*- and *p*-methylbenzylamine derivatives were obtained, but *p*-derivatives were formed predominantly (entries 7 and 13). The *m*-methoxy- and *m*-fluorophenyltriazenes produced *o*-substitut-

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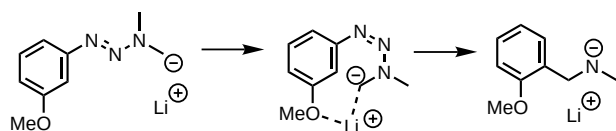
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Table 1. Synthesis of benzylamine derivatives.<sup>[a]</sup>

| Entry | X             | R                                  | Electrophile       | X'                             | E           | Yield [%] |
|-------|---------------|------------------------------------|--------------------|--------------------------------|-------------|-----------|
| 1     | H             | H                                  | H <sub>2</sub> O   | H                              | H           | 57        |
| 2     | H             | H                                  | <i>n</i> BuBr      | H                              | <i>n</i> Bu | 78        |
| 3     | H             | H                                  | Boc <sub>2</sub> O | H                              | Boc         | 81        |
| 4     | H             | Me                                 | Boc <sub>2</sub> O | H                              | Boc         | 47        |
| 5     | H             | -(CH <sub>2</sub> ) <sub>2</sub> - | Boc <sub>2</sub> O | H                              | Boc         | 69        |
| 6     | <i>o</i> -Me  | H                                  | H <sub>2</sub> O   | <i>m</i> -Me                   | H           | 74        |
| 7     | <i>m</i> -Me  | H                                  | H <sub>2</sub> O   | <i>o</i> -, <i>p</i> -Me (1:2) | H           | 71        |
| 8     | <i>p</i> -Me  | H                                  | H <sub>2</sub> O   | <i>m</i> -Me                   | H           | 95        |
| 9     | <i>p</i> -Me  | H                                  | Boc <sub>2</sub> O | <i>m</i> -Me                   | Boc         | 96        |
| 10    | <i>p</i> -MeO | H                                  | Boc <sub>2</sub> O | <i>m</i> -MeO                  | Boc         | 78        |
| 11    | <i>p</i> -TMS | H                                  | Boc <sub>2</sub> O | <i>m</i> -TMS                  | Boc         | 70        |
| 12    | <i>p</i> -F   | H                                  | Boc <sub>2</sub> O | <i>m</i> -F                    | Boc         | 89        |
| 13    | <i>m</i> -Me  | H                                  | Boc <sub>2</sub> O | <i>o</i> -, <i>p</i> -Me (1:2) | Boc         | 90        |
| 14    | <i>m</i> -MeO | H                                  | Boc <sub>2</sub> O | <i>o</i> -MeO                  | Boc         | 70        |
| 15    | <i>m</i> -F   | H                                  | Boc <sub>2</sub> O | <i>o</i> -F                    | Boc         | 41        |
| 16    | <i>m</i> -TMS | H                                  | Boc <sub>2</sub> O | <i>p</i> -TMS                  | Boc         | 81        |

[a] Boc = *tert*-butoxycarbonyl; TMS = trimethylsilyl.

ed benzylamines in good to moderate yields (entries 14 and 15). For X = MeO, the result is explained by the chelate effect shown in Scheme 1. In the other case, the chelating and inductive effects of the F atom cause attack of the anion at that position. On the other hand, *m*-trimethylsilylphenyltriazene gave *p*-trimethylsilylbenzylamine as the sole product (entry 16), whereby steric hindrance between the trimethylsilyl group and the carbanion resulted in selectivity. Thus, the regioselectivities of the carbon–carbon bond formation are attributable to the electronic and steric features of the substituents on the aromatic ring.



Scheme 1. Chelate effect.

We obtained additional significant results by further investigation into the course of these reactions. Treating 1-aryl-3,3-dialkyltriazenes with substituents at the 2- and 6-positions of the aryl groups with *n*BuLi gave good yields of dearomatized heterocyclic compounds [Eq. (2)].<sup>[11]</sup> The results are summarized in Table 2. For R' = Me, two diastereomers were obtained (entries 2 and 6). In contrast, triazenes derived from pyrrolidine (entries 3 and 7) and piperidine (entries 4 and 8) gave single diastereomers.

On the basis of the above results, we propose the reaction mechanism shown in Scheme 2. Deprotonation occurs at the C atom  $\alpha$  to N3. Nucleophilic attack of the resulting anion at the *o*-position of the aryl

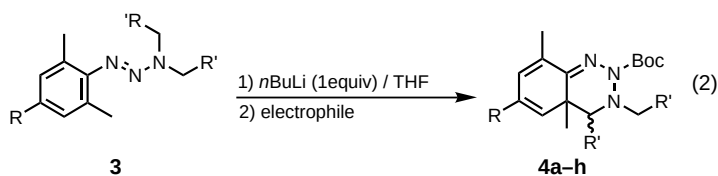


Table 2. Synthesis of dearomatized compounds.

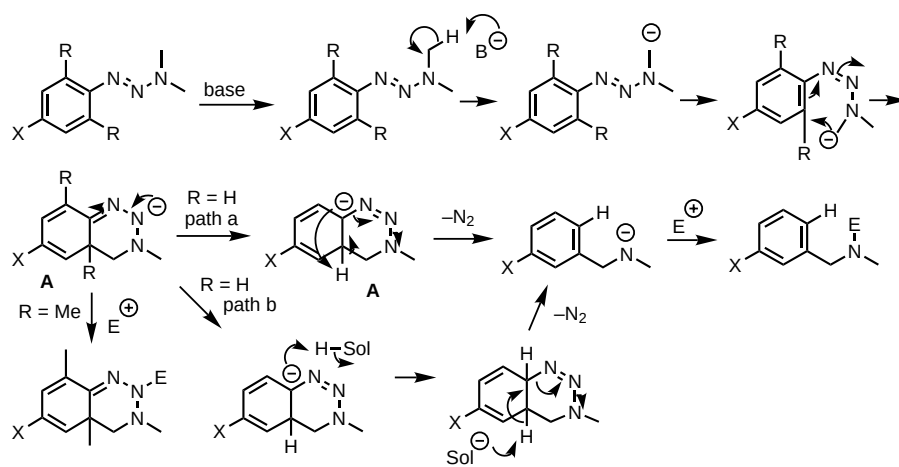
| Entry | R  | R'                                 | Product   | Yield [%] <sup>[a]</sup> |
|-------|----|------------------------------------|-----------|--------------------------|
| 1     | H  | H                                  | <b>4a</b> | 73                       |
| 2     | H  | Me                                 | <b>4b</b> | 64 (1:2.9)               |
| 3     | H  | -(CH <sub>2</sub> ) <sub>2</sub> - | <b>4c</b> | 75                       |
| 4     | H  | -(CH <sub>2</sub> ) <sub>3</sub> - | <b>4d</b> | 58                       |
| 5     | Me | H                                  | <b>4e</b> | 65                       |
| 6     | Me | Me                                 | <b>4f</b> | 52 (1:5)                 |
| 7     | Me | -(CH <sub>2</sub> ) <sub>2</sub> - | <b>4g</b> | 85                       |
| 8     | Me | -(CH <sub>2</sub> ) <sub>3</sub> - | <b>4h</b> | 63                       |

[a] The values in parentheses indicate diastereoselectivity. The ratio of diastereomers was determined by <sup>1</sup>H NMR spectroscopy.

group is followed by dearomatization. For R = H, two possible routes for further reaction were considered. Path a involves an intramolecular 1,2-proton shift and elimination of N<sub>2</sub>. In path b, the proton that originated from the solvent is incorporated into the anion, after which a proton is abstracted by the anion of the solvent (HSol). For R = Me, the proton shift analogous to path a and the proton exchange as in path b can not proceed, because the dearomatized intermediate **A** has no such proton available for the rearomatization step. Consequently, the *N*-anion **A** immediately reacts with an electrophile to give a tetrahydrobenzotriazine derivative.

In conclusion, we found a new carbon–carbon bond-forming reaction by intramolecular nucleophilic attack of carbanions generated from 1-aryl-3,3-dialkyltriazenes. These reactions provide an alternative method for the preparation of benzylamine derivatives and dearomatized compounds. Further studies are in progress.

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Scheme 2. Proposed mechanism.

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## Fluorescent Deazaflavin – Oligonucleotide Probes for Selective Detection of DNA

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Arrays of oligonucleotide probes (DNA chips) immobilized on glass or silicon surfaces have emerged as powerful new tools for the analysis of DNA and RNA.<sup>[1]</sup> These specific DNA sensors operate through hybridization reactions which are based on the mutual recognition of two complementary nucleic acid strands that establish hydrogen bonds between their nucleic bases. Hybridization is most commonly assayed by fluorescence, and hence requires that fluorophore labels are covalently attached to the DNA target fragments to be analyzed.

This technology, however, is still fraught with a number of drawbacks and requires new developments. For example, it is still difficult to assess the quality of the oligonucleotides attached to the surface. The homogeneity and the reproducibility of the procedures for preparing the DNA-functionalized surfaces, and consequently the DNA surface density, are difficult to control. Furthermore the polymerase chain reaction (PCR) step, which serves to amplify the DNA targets, and the subsequent chemical step, for the attachment of the fluorophore to the target DNA, are responsible for significant modifications in the relative proportions of the different populations of the nucleic acids to be analyzed.

We propose that some of these problems might be simply solved if the detection label (here a fluorophore) is incorporated on the array capture DNA strand and not on the target to be detected. This strategy might have many advantages. First it greatly reduces the number of manipulations of the targets. Second, it provides a way to control the quality of the DNA array (by using standard fluorescence scanners) in the absence of the targets. Such an array requires that: 1) the fluorescence is not quenched by interaction of the fluorophore with the surface; 2) the label on the probe does not affect its affinity for its complementary oligonucleotide; and 3) the fluorescence is significantly changed as a specific consequence of hybridization of the functionalized DNA

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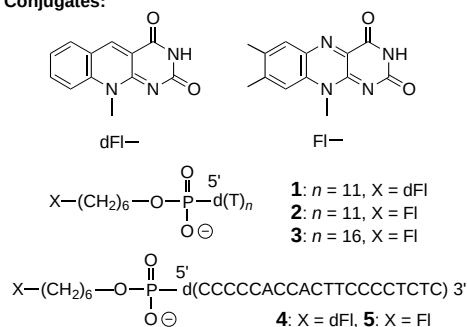
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probe to its complementary target, so that DNA recognition can be detected.

Here we report that flavins and deazaflavins provide the first examples of such a label. Flavins and deazaflavins exhibit a bright blue or green fluorescence at 520–540 and 450–460 nm, respectively, in aqueous solutions, with deazaflavins giving larger fluorescence intensities. We have recently reported an efficient method for the synthesis of stable flavin–oligonucleotide conjugates that is also used here for the preparation of new deazaflavin–oligonucleotide conjugates.<sup>[2]</sup> Furthermore, these conjugates are stable to UV irradiation.<sup>[3]</sup> Preliminary results demonstrate here that these molecules are able to hybridize to a complementary oligonucleotide target both in solution and on solid support, and that the hybridization can be detected by a dramatic quenching of the probe fluorescence.

The deazaflavin–oligonucleotide conjugates **1** and **4** (Scheme 1 and 2) were synthesized from the corresponding oligo-2'-deoxynucleotides prepared by the phosphoramidite automated method with standard building phosphoramidites

#### Conjugates:



#### Targets:

**5'** d(CTCATCGTGT(A)<sub>n</sub>GGCAGTACTGGAAGGGGCTAATTCT) 3'  
**6:**  $n = 11$ , **7:**  $n = 16$

**ICAM20:** d(GCCTGATGAGAGGGGAAGTGGTGGGGGAGACATAGCCACC)

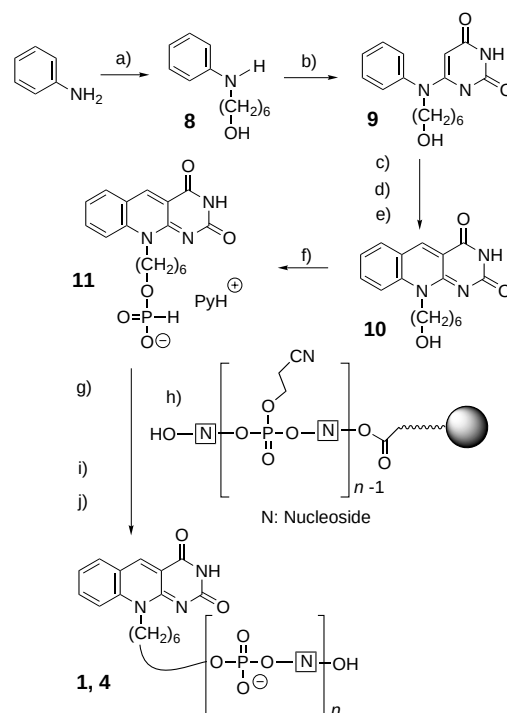
**ICAM17:** d(GCCTGATGAGAGGGGAAGTGGTGGCCAGACATAGCCACC)

**ICAM14:** d(GCCTGATGAGAGGGGAAGTGGATTCCAGACATAGCCACC)

**ICAM18:** d(GCCTGATGAGAGGGGACTTGGTGGGGGAGACATAGCCACC)

Scheme 1. Oligonucleotide conjugates of 5-deazaflavin (dFI) and flavin (FI), as well as their corresponding targets.

(see Supporting Information). The 5'-hydroxyl group of the oligonucleotide attached to the solid support was coupled to the 5-deazaflavin H-phosphonate derivative **11** (synthesized from aniline and 6-chlorouracil) after activation with adamantanecarboxylic acid chloride (Scheme 2).<sup>[4]</sup> Oxidation of the conjugate on the solid support with iodine and then cleavage and deprotection with sodium hydroxide afforded the conjugates **1** and **4** in high yields (60 and 53%, respectively). The conjugates **1** and **4** were characterized by <sup>1</sup>H and <sup>31</sup>P NMR spectrometry, mass spectrometry (matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) and electrospray ionization (ESI)), and absorption spectrophotometry.



Scheme 2. Synthesis of the 5-deazaflavin–oligonucleotide conjugates: a)  $\text{HO}(\text{CH}_2)_6\text{Cl}$ , 120 °C, 74 %; b) 6-chlorouracil/ $\text{H}_2\text{O}/\text{EtOH}$ , reflux, 65 %; c)  $\text{Ac}_2\text{O}/\text{Py}$ , RT; d)  $\text{DMF}/\text{POCl}_3$ , 100 °C; e)  $\text{KOH}/\text{EtOH}$ , RT, 70 % for the three (c–e) steps; f)  $\text{H}_3\text{PO}_3/\text{TPSO}_2\text{Cl}/\text{Py}$ , 85 %; g) adamantanecarboxylic acid chloride/3'-acetylthymidine/ $\text{Py}$ ; h) nucleoside, coupling step; i)  $\text{I}_2/\text{THF}/\text{Et}_3\text{N}$ ; j)  $\text{NaOH}/\text{H}_2\text{O}/\text{CH}_3\text{OH}$ . Py = pyridine, TP = 2,4,6-trisopropylbenzene.

The fluorescence emission spectrum of the deazaflavin moiety of the conjugates was comparable to that of the free deazaflavin, with a peak maximum at 450 nm (excitation at 396 nm) and a high quantum yield of 0.26, which is comparable to or even better than that of standard fluorophores such as Alexa and Cyanine dyes. Furthermore, the observation that the duplex has the same melting temperature ( $T_m = 62$  °C, NaCl 10 mM) whether the probe contained the tag or not<sup>[5]</sup> indicates that the deazaflavin tag had no effect on the stability of the duplex formed between the oligonucleotide probe and a 42-mer oligonucleotide target, **ICAM20**, which contains the 20-mer complementary sequence (Scheme 1).

Figure 1 shows a representative experiment in which the addition of increasing amounts of the target oligonucleotide **ICAM20** resulted in a decay of the fluorescence intensity of compound **4** at 450 nm to less than 5 % of the initial value after the addition of one equivalent of **ICAM20**. Control experiments, carried out either by addition of **ICAM20** in the presence of one equivalent of the free deazaflavin to an oligonucleotide identical to **4** but lacking the deazaflavin group or by addition of increasing amounts of a 45-mer oligonucleotide target with no complementary sequence to a solution of conjugate **4**, resulted in no variation in the fluorescence of the deazaflavin unit. In the case of conjugate **1**, quenching also occurred upon hybridization with target **6** ( $T_m = 43$  °C, NaCl 1 M), and the fluorescence was shown to be fully restored upon heating to a temperature that allowed dissociation of the complex. Several cycles of hybridization/

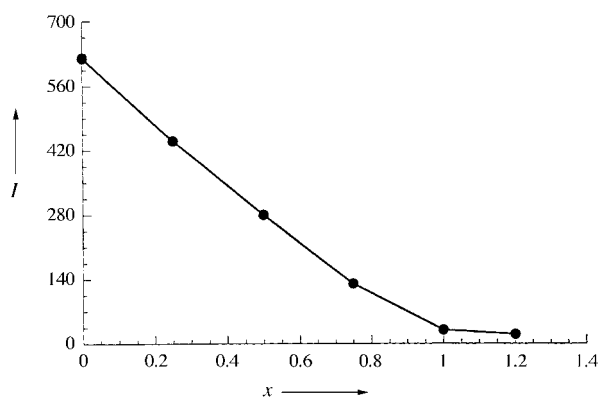


Figure 1. Effect of the addition of increasing amounts of **ICAM20** on the fluorescence intensity ( $I$ ) of conjugate **4** ( $2\ \mu\text{M}$  in  $50\ \text{mM}$  tris(hydroxymethyl)aminomethane-HCl (Tris-HCl), pH 7.5,  $10\ \text{mM}$  NaCl,  $25^\circ\text{C}$ ) at  $450\ \text{nm}$  (excitation at  $396\ \text{nm}$ ).  $x$  represents the target/**4** ratio.

melting, as monitored by fluorescence spectroscopy, were successfully performed. All these highly reproducible results showed that the fluorescence quenching observed here was a specific property of a deazaflavin moiety attached to an oligonucleotide on hybridization to the complementary strand.

Similar results were obtained with the flavin-oligonucleotide conjugates **2**, **3**, and **5** (synthesized as described previously<sup>[2]</sup>) and using the oligonucleotides **6**, **7**, and **ICAM20** as the complementary strands, respectively. In the case of probe **3**, sequence variations in the proximity of the flavin moiety (GC, CG, or CC in place of the GG doublet adjacent to the polyA strand) in the target **7** had no effect on the quenching efficiency. The results taken together indicate that the extent of fluorescence quenching, with both deazaflavin and flavin as markers, does not depend on particular target lengths and sequences. This observation seems to rule out specific interactions, such as hydrogen bonding between the probe fluorophore and bases of the target, as the origin of the quenching.

An interesting observation is shown in the Stern–Volmer representation  $I_0/I(x)$  plotted as a function of increasing amounts  $x$  of various targets (Figure 2). The results indicate that fluorescence quenching makes it possible, with a given

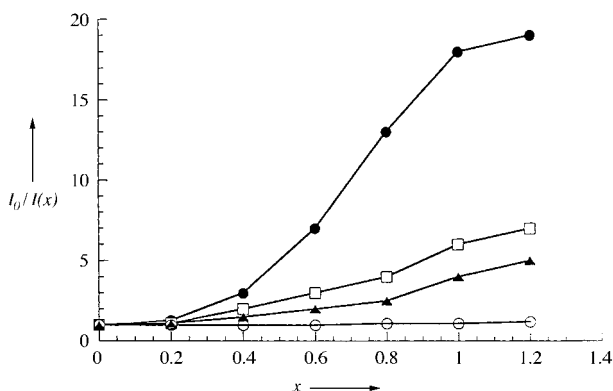


Figure 2. Effect of the addition of increasing amounts of different targets ( $\bullet$  **ICAM20**,  $\square$  **ICAM18**,  $\blacktriangle$  **ICAM17**,  $\circ$  **ICAM14**) on the fluorescence of conjugate **4** under the same conditions as for Figure 1.  $I_0$  represents the initial fluorescence intensity of **4** and  $I(x)$  its intensity after the addition of  $x$  equivalents of the target oligonucleotide.

probe, to discriminate targets of variable complementarity. Significantly decreased quenching occurs because of decreased base pairing, which occurs as a result of mutations at the 3' part of the sequence facing the 5' part of conjugate **4** to which the deazaflavin moiety is attached (compare **ICAM20** to **ICAM17** and **ICAM14**) or because of mutations in the interior of the DNA targets (compare **ICAM20** to **ICAM18**). This effect probably results from a combination of an increased distance between the deazaflavin and the target and decreased amounts of the hybridized probe at equilibrium, and hence might have applications for the detection of mutations in solution.

Since deazaflavin-oligonucleotide conjugates might serve as fluorescent probes in the new concept of DNA microarrays proposed here, we finally checked whether the same duplex-specific quenching effect occurred on a solid surface. In this experiment  $20\ \mu\text{L}$  of a  $10\ \mu\text{M}$  solution of conjugate **4** were deposited at several places on a glass slide and then dried. By shining a mercury  $100\ \text{W}$  lamp of an epi-fluorescence microscope through an appropriate dichroic mirror for excitation at  $396\ \text{nm}$ , fluorescence emission could be detected with a high sensitivity spectrophotometer through an optical fiber mounted on the microscope in place of the camera.<sup>[6]</sup> This arrangement allowed the detection of a well-resolved signal at  $500\ \text{nm}$  (intensity:  $1100$  arbitrary units) corresponding to the fluorescence of the deazaflavin moiety of conjugate **4** on the glass surface. Duplex formation was allowed for  $10\ \text{min}$  on several spots after the addition of five equivalents ( $20\ \mu\text{L}$  in  $0.1\ \text{M}$  NaCl) of the complementary oligonucleotide **ICAM20**. An assay of the fluorescence of each spot after drying the surface revealed a reproducible large quenching (intensity:  $100$  arbitrary units). No quenching of fluorescence could be detected when oligonucleotides with no complementary sequence were instead added on fluorescent spots under the same conditions and then dried. This result demonstrates that quenching was specific for the hybridized probe and not the result of some unspecific effect of the added oligonucleotide.

In conclusion, we propose that flavins or deazaflavins might be suitable fluorescent markers for oligonucleotide probes to be used in DNA microarrays. First, these markers do not affect the affinity for the complementary strand. Second, their fluorescence is also detectable on a solid surface by fluorescence scanners, which thus provides a means of controlling the quality of the array. Third, their fluorescence is specifically quenched upon hybridization to a complementary sequence, thus allowing DNA detection. Fourth, the hybridization/fluorescence quenching is reversible. Even though, in general, a generation of a signal is preferred to a decay, the concept of labeled DNA arrays proposed here is also likely to be applicable and to provide significant advantages.

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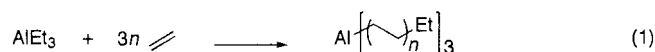
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## Iron-Catalyzed Polyethylene Chain Growth on Zinc: Linear $\alpha$ -Olefins with a Poisson Distribution\*\*

George J. P. Britovsek, Steven A. Cohen, Vernon C. Gibson,\* Peter J. Maddox, and Martin van Meurs

Fifty years ago Ziegler and co-workers reported the *Aufbaureaktion* for alkylaluminum compounds.<sup>[1]</sup> This reaction involves a stepwise insertion of ethylene into the Al–C bonds of, for example, triethylaluminum to give long-chain trialkylaluminum compounds [Eq. (1)]. Today, this chain-growth reaction is commercially exploited for the synthesis of linear  $\alpha$ -olefins and primary alcohols from ethylene.<sup>[2]</sup>

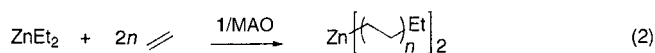
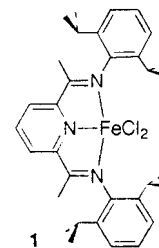


Subsequently, Ziegler and co-workers discovered the effect of transition metals such as colloidal nickel on this reaction, which suppressed chain growth to give only butene.<sup>[3]</sup> The elucidation of this “nickel effect”, and the subsequent screening of the periodic table for the effects of other metals led to the discovery of the first transition metal catalyzed ethylene polymerization.<sup>[4]</sup>

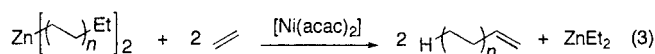
In their early reports,<sup>[4]</sup> Ziegler and co-workers generally described the aluminum compound as the polymerization catalyst, with the transition metal compound functioning as the cocatalyst, and therefore considered the whole chain-

growth process to occur at the aluminum centers or, in other words, a transition metal catalyzed “*Aufbaureaktion*”. Later it was realized that in these polymerization systems, the polymer chain actually grows on the transition metal and not on the aluminum center. But, to complicate matters, in recent years it has been observed that, for certain early as well as late transition metal polymerization catalysts, under certain conditions, the polymer chain is transferred to the aluminum centers during the polymerization reaction, a process that is referred to as *chain transfer to aluminum*. This reaction is sometimes the only transfer process,<sup>[5]</sup> but more often it occurs alongside the more common  $\beta$ -H transfer process.<sup>[6–9]</sup> If chain transfer to aluminum constitutes the sole transfer mechanism, and the exchange of the growing polymer chains between the transition metal and the aluminum centers is very fast and reversible, the polymer chains will appear to be growing on the aluminum centers. This can then reasonably be described as a transition metal catalyzed chain growth reaction on aluminum or, using Ziegler’s terminology, a transition metal catalyzed “*Aufbaureaktion*”. An attractive manifestation of this type of chain-growth reaction (catalyzed or uncatalyzed) is a Poisson distribution of main group alkyl products, as opposed to the Schulz–Flory distribution of olefinic products that arises when  $\beta$ -H transfer accompanies propagation.<sup>[10]</sup>

Systems where these criteria are fulfilled, or are close to being fulfilled, have been described for transition metal and rare-earth metallocenes (on Al and Mg)<sup>[11–14]</sup> and recently for half-sandwich complexes of chromium (on Al).<sup>[16]</sup> Here we report the first highly active chain-growth process on zinc, catalyzed by bis(imino)pyridineiron catalyst **1** [Eq. (2)]. We also describe a nickel-catalyzed



displacement of the grown alkyl chain, in the presence of ethylene, to regenerate diethylzinc and to give a Poisson distribution of  $\alpha$ -olefins [Eq. (3); acac = acetylacetonate].



In the absence of  $\text{ZnEt}_2$ , a polymerization system containing **1** (5  $\mu\text{mol}$ ) and 100 equivalents of methylalumoxane (MAO) generates high molecular weight polyethylene with a broad molecular weight distribution (Table 1, Figure 1). A small amount of a low molecular weight fraction is also obtained, due to chain transfer to the  $\text{AlMe}_3$  present in MAO. An increased proportion of low molecular weight material is obtained upon addition of 100 equivalents of  $\text{ZnEt}_2$  (run 2, Table 1). At 500 equivalents of  $\text{ZnEt}_2$  (2.5 mmol) a very narrow molecular weight distribution product results ( $M_n = 700$ ,  $M_w = 800$ ,  $M_w/M_n = 1.1$ ). The polymer yield after hydro-

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Table 1. Polymerization runs using **1** with various amounts of ZnEt<sub>2</sub>.<sup>[a]</sup>

| Run | ZnEt <sub>2</sub><br>[equiv] | Yield<br>[g] | Activity<br>[g mmol h <sup>-1</sup> ] | M <sub>n</sub> | M <sub>w</sub> | PDI  | Vinyl<br>chain<br>ends | Saturated<br>chain<br>ends |
|-----|------------------------------|--------------|---------------------------------------|----------------|----------------|------|------------------------|----------------------------|
| 1   | 0                            | 3.01         | 1204                                  | 10000          | 192000         | 19.2 | 0.20                   | 2.69                       |
| 2   | 100                          | 4.86         | 1944                                  | 3000           | 110000         | 36.8 | 0.18                   | 8.05                       |
| 3   | 500                          | 3.51         | 1404                                  | 700            | 800            | 1.1  | 0.23                   | 38.71                      |

[a] Conditions: toluene solution, 5 μmol **1**, 100 equivalents of MAO, RT, 1 bar ethylene, 30 min.

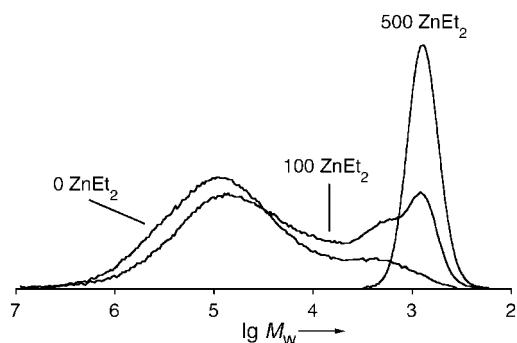


Figure 1. GPC traces of the polyethylene samples obtained by using different ratios of ZnEt<sub>2</sub> to catalyst system **1**/MAO.

lytic workup was 3.51 g, corresponding to an activity of 1404 g mmol<sup>-1</sup> h<sup>-1</sup> based on iron. Analysis of the polymer by NMR spectroscopy revealed a fully saturated linear alkane product.

The narrow molecular weight distribution is reminiscent of a living-polymerization system and lies in stark contrast to the broad molecular weight distribution typically observed with bis(imino)pyridineiron catalysts.<sup>[9]</sup> The amount of polyethylene produced is 5 mmol (yield/M<sub>n</sub>) corresponding to two alkyl chains per zinc center. This surprising result led us to conclude that long-chain dialkylzinc species had been produced by an iron-catalyzed chain-growth reaction on zinc, which after hydrolysis yielded linear alkanes. By contrast, the insertion of ethylene into a Zn–C bond in the absence of a catalyst is very slow and stops after one insertion.<sup>[16, 17]</sup> The insertion of substituted alkenes into the Zn–C bond (carbocation) has been catalyzed by zirconium<sup>[18]</sup> or palladium catalysts<sup>[19]</sup> but also in these cases only a single insertion is generally observed.

During a typical polymerization experiment using **1**/MAO as the catalyst, but without diethylzinc (run 1, Table 1), the onset of polyethylene precipitation occurs within the first minute. In the presence of 500 equivalents of diethylzinc, the reaction solution remains clear for an extended period (ca. 15 min under the conditions used here) until an abrupt precipitation occurs when the solubility-limiting chain length (M<sub>n</sub> ≈ 700) has been reached. Liquid samples were taken at two- to three-minute time intervals and, after hydrolysis, were analyzed by GC (Figure 2). The peak maximum of the Poisson distribution shifts to higher carbon number (*n*) with increased time, in an analogous fashion to the increase in M<sub>n</sub> with time typical of living-polymerization systems.

Instead of hydrolysis, the grown alkyl chains can also be displaced from the zinc centers by an olefin-exchange reaction

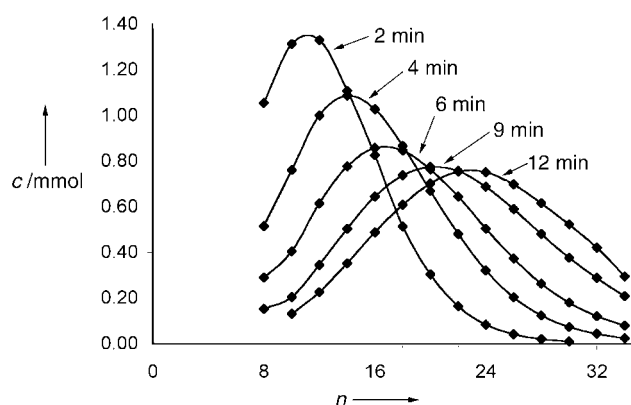


Figure 2. Alkane distributions obtained from the chain-growth reaction after different time intervals. *n* = carbon number.

that can be catalyzed by nickel complexes such as [Ni(acac)<sub>2</sub>].<sup>[20]</sup> After separation from the iron catalyst, the grown alkylzinc compounds were exposed to ethylene (1 bar) in the presence of 5% [Ni(acac)<sub>2</sub>]. Analysis of the product by GC revealed clean formation of linear α-olefins, with a Poisson distribution of chain lengths.

To the best of our knowledge, these results represent the first observation of a catalyzed chain-growth reaction on zinc. Significantly, the chain-growth process occurs at an ethylene pressure of 1 bar and at room temperature, contrasting the more forcing conditions required for the uncatalyzed “Aufbaureaktion” (typically 100 °C, 100 bar ethylene). We are presently investigating the effect of other alkyl metal compounds in this reaction as well as other transition metal catalysts potentially suited to catalyzing the chain-growth reaction. Preliminary results indicate that Group 4 metallocenes and nickel α-diimine catalysts can also give rise to efficient chain transfer to zinc.

## Experimental Section

**2,6-Bis[1-(2,6-diisopropylphenyl)imino]ethylpyridineiron(II) chloride (**1**)** was prepared according to an established procedure.<sup>[11]</sup> MAO (10% in toluene) was obtained from Witco. Diethylzinc was used as a toluene solution (1.1M), obtained from Aldrich. Undecane was obtained from Aldrich and distilled over CaH<sub>2</sub> prior to use.

**Chain transfer experiments:** A catalyst solution was prepared from **1** (30 mg, 0.05 mmol), MAO (3 mL, 100 equiv), and toluene (22 mL). The clear orange solution was stirred for 5 min at room temperature. Aliquots of 2.5 mL of this solution (5 μmol **1**) were placed in four separate Schlenk flasks, each containing toluene (50 mL). After the addition of various amounts of ZnEt<sub>2</sub>, (0, 100, and 500 equiv) the resulting yellow solutions were placed under ethylene (1 bar). The reactions were terminated after 30 min by the addition of dilute hydrochloric acid solution (1M). The products were filtered, washed with methanol, and dried at 50 °C in vacuum.

**Chain-growth experiments:** A catalyst solution was prepared from **1** (6 mg, 0.01 mmol), MAO (0.6 mL, 100 equiv), and toluene (24.4 mL). The clear orange solution was stirred for 5 min at room temperature. An aliquot of 2.5 mL of this solution (1 μmol **1**) was added to a ZnEt<sub>2</sub> solution (2.5 mL of 1.1M solution) in toluene (50 mL) under ethylene (1 bar). Time-dependent experiments were carried out by taking 1 mL samples (five in total) over a 12 minute period. The samples were immediately quenched with dilute HCl solution (1M), dried with MgSO<sub>4</sub>, and filtered. Samples were analyzed by GC, using undecane as internal standard.

**Displacement experiments:** A chain-growth experiment was carried out using **1** (2 μmol) and ZnEt<sub>2</sub> (3.5 mL of a 1.1M solution in toluene) in toluene



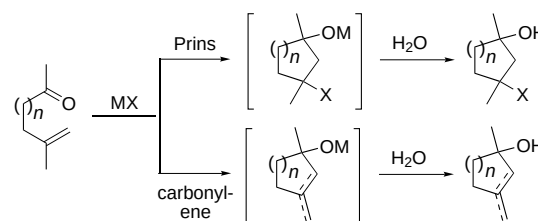
(50 mL) at room temperature and an ethylene pressure of 1 bar. After 8 min, the reaction mixture was transferred to another flask containing a slurry of dried silica (1.5 g) in toluene (10 mL) and MAO (1 mL). After stirring at room temperature for 15 min, the mixture was filtered into another flask containing  $[\text{Ni}(\text{acac})_2]$  (90 mg, 0.35 mmol) in toluene. After the mixture had been stirred at room temperature for 30 min under an ethylene pressure of 1 bar, the reaction was quenched by the addition of dilute HCl (50 mL of a 1M solution). After separation of the phases, the organic layer was dried over  $\text{MgSO}_4$  and the product was analyzed by GC.

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## Stereoselective Prins Cyclizations of $\delta,\epsilon$ -Unsaturated Ketones to *cis*-3-Chlorocyclohexanols with $\text{TiCl}_4$ \*\*

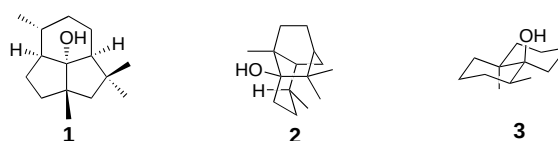
Chad E. Davis and Robert M. Coates\*

The closely related Prins and carbonyl-ene cyclizations have proven to be useful transformations for forming five-membered, six-membered, and larger rings in the synthesis of carbocyclic natural products.<sup>[1, 2]</sup> These similar annulation methods both involve initial electrophilic attack of an activated carbonyl group onto an olefin, followed by either nucleophilic capture or proton elimination (Scheme 1,  $\text{MX}$  = Lewis acid).



Scheme 1. Lewis acid mediated Prins and carbonyl-ene cyclizations of unsaturated ketones.

Although Lewis acid mediated Prins cyclizations of aldehydes<sup>[1, 3]</sup> and trifluoromethyl ketones<sup>[4, 5]</sup> are rather well documented in the literature, to our knowledge only a few examples of nucleophilic capture products from non-fluorinated ketones have been reported.<sup>[6]</sup> This transformation would afford an attractive synthetic approach for the construction of hindered tertiary alcohols, a structural motif common in terpene natural products such as presilphiperfolan-8-ol (**1**), patchouli alcohol (**2**), and geosmin (**3**).<sup>[7]</sup> Here we report  $\text{TiCl}_4$ -mediated stereoselective Prins cyclizations of  $\delta,\epsilon$ - and  $\epsilon,\zeta$ -unsaturated ketones<sup>[8]</sup> to *cis*-3-chlorocyclohexanols as well as comparisons with the corresponding reactions in which HCl is used.



A series of  $\delta,\epsilon$ -unsaturated ketones prepared by the Sakurai<sup>[9]</sup> addition of allyl- or methallylsilanes to the requisite enone underwent cyclization in the presence of  $\text{TiCl}_4$  (1.0 equiv) or HCl (0.9 equiv to large excess) in  $\text{CH}_2\text{Cl}_2$  at

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

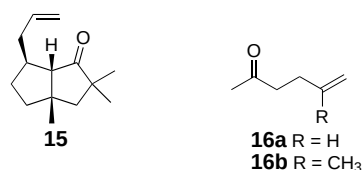
Table 1. Conditions and isomeric chlorohydrin products formed in Prins-type cyclizations of allyl and methallyl ketones with  $\text{TiCl}_4$  and  $\text{HCl}$ .

| Entry | Keto Olefins |    |            | Conditions <sup>[a]</sup><br>Reagent, <i>t</i> [min] | Structure | Chlorohydrin Products <sup>[b,c]</sup> |              |               | Yield [%] | Olefin Products<br>Yield [%] |
|-------|--------------|----|------------|------------------------------------------------------|-----------|----------------------------------------|--------------|---------------|-----------|------------------------------|
|       | Structure    | R  | No.        |                                                      |           | <i>cis</i>                             | <i>trans</i> | Ratio         |           |                              |
| 1     |              | H  | <b>4a</b>  | $\text{TiCl}_4$ , 0.5                                |           | <b>5a</b>                              | <b>6a</b>    | 7:1           | 62        | –                            |
| 2     |              |    |            | 15                                                   |           |                                        |              | 8:1           | 72        | –                            |
| 3     |              |    |            | $\text{HCl}$ , 5                                     |           |                                        |              | < 1:99        | 64        | –                            |
| 4     |              | Me | <b>4b</b>  | $\text{TiCl}_4$ , 0.25                               |           | <b>5b</b>                              | <b>6b</b>    | 13:1          | 55        | 12                           |
| 5     |              |    |            | 0.5 <sup>[d]</sup>                                   |           |                                        |              | 4:1           | 65        | 28                           |
| 6     |              |    |            | $\text{HCl}$ , 0.5                                   |           |                                        |              | < 1:99        | 50        | 41                           |
| 7     |              | H  | <b>7a</b>  | $\text{TiCl}_4$ , 5                                  |           | <b>8a</b>                              | <b>9a</b>    | 6:1           | 59        | –                            |
| 8     |              |    |            | 15                                                   |           |                                        |              | 5:1           | 66        | –                            |
| 9     |              |    |            | $\text{HCl}$ , 22 <sup>[e]</sup>                     |           |                                        |              | (no reaction) |           |                              |
| 10    |              | Me | <b>7b</b>  | $\text{TiCl}_4$ , 0.5                                |           | <b>8b</b>                              | <b>9b</b>    | 12:1          | 93        | –                            |
| 11    |              |    |            | 0.5 <sup>[d]</sup>                                   |           |                                        |              | 10:1          | 91        | 3                            |
| 12    |              |    |            | $\text{HCl}$ , 45                                    |           |                                        |              | 1:3           | 51        | 33                           |
| 13    |              | H  | <b>10a</b> | $\text{TiCl}_4$ , 45                                 |           | <b>11</b>                              | <b>12</b>    | 1:4           | 68        | 32                           |
| 14    |              |    |            | 0.5                                                  |           |                                        |              | 1.3:1         | 63        | 8                            |
| 15    |              |    |            |                                                      |           |                                        |              |               |           | 48                           |
| 16    |              | Me | <b>10b</b> | $\text{TiCl}_4$ , 0.5                                |           | <b>14</b>                              |              |               | 69        | 11                           |
| 17    |              |    |            | 0.5 <sup>[d]</sup>                                   |           |                                        |              |               | 87        | 11                           |

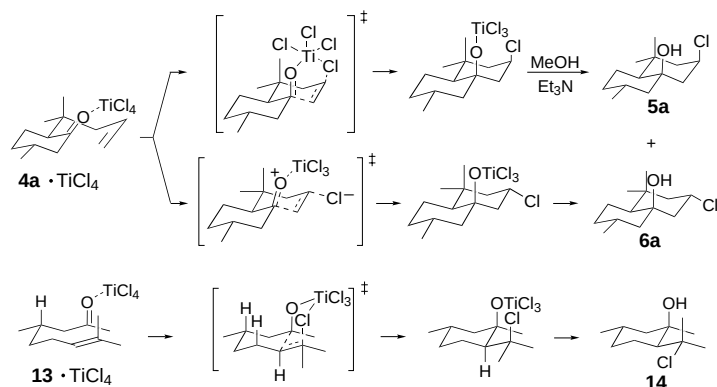
[a]  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  unless otherwise noted. [b] *cis* and *trans* refer to Cl–OH relationship. [c] Ratios and yields of unstable tertiary chlorohydrins determined by  $^1\text{H}$  NMR analysis of the crude product. [d] Toluene,  $-78^\circ\text{C}$ . [e]  $-20^\circ\text{C}$ , 15 min; RT, 7 min. [f]  $\text{Et}_2\text{O}$ , RT.

$-78^\circ\text{C}$  (Table 1). The product distributions were determined by quantitative  $^1\text{H}$  NMR analysis prior to chromatographic purification. The structure and stereochemistry of the cyclization products were established by a combination of NMR analysis, X-ray crystallography,<sup>[10]</sup> and chemical conversions.<sup>[11]</sup> Reductive dechlorination ( $\text{Bu}_3\text{SnH}$ , AIBN,  $\text{PhH}$ , reflux) of secondary epimeric chlorohydrins afforded the same tertiary alcohol whereas base-induced elimination of epimeric tertiary chlorides provided correlation to olefins.

The results indicate that the  $\text{TiCl}_4$ -mediated cyclizations are selective for the formation of *cis*-chlorohydrins, whereas the use of  $\text{HCl}$  gave the *trans*-chlorohydrin with variable selectivity and higher proportions of cyclic olefins. Higher yields and increased selectivities were obtained in dichloromethane or toluene than in pentane. The yields and isomer ratios from cyclizations of ketones **4a** and **7a** did not vary appreciably with prolonged reaction times, which indicates the stability of the products under the reaction conditions. Interestingly, keto olefins **15**, **16a** and **16b** were all inert to the  $\text{TiCl}_4$  conditions. The failure of the allyl bicyclo[3.3.0]octanone (**15**) to undergo cyclization may be a reflection of the high degree of strain associated with the tricyclo[5.3.1.0<sup>4,11</sup>]undecane ring system.



The *cis* selectivity observed in the  $\text{TiCl}_4$ -mediated cyclizations may be rationalized either by a pericyclic mechanism that proceeds through a six-membered cyclic transition state (Scheme 2) or by suprafacial ion pair formation and collapse. In the former model, a ketone– $\text{TiCl}_4$  complex could undergo



Scheme 2. Pericyclic mechanisms proposed for *cis* selective Prins cyclizations with  $\text{TiCl}_4$ .

concerted suprafacial addition across the proximal double bond by way of a highly polarized boatlike or chairlike array. Alternatively the predominant formation of *cis*-chlorohydrin could be explained by a nonconcerted mechanism in which intramolecular alkylation of the double bond generates transient carbocation ion pairs such as  $\text{R}^+/\text{ROTiCl}_4^-$  or  $\text{R}^+/\text{Cl}^-$  that collapse to the covalent *cis*-chlorotitanate products

faster than rearrangement to the *trans* ion pair stereoisomers occurs. The much faster rates ( $\geq 10$ –20 times) of the methallyl ketones reveals substantial carbocation character in either case.

This hydroxyalkylation transformation constitutes a *syn* addition to the C–C double bond. Although this *syn* selectivity is not without precedent,<sup>[12]</sup> it contrasts with the predominant *anti* selectivity observed in cyclodecenone cyclizations.<sup>[6a,b]</sup> The *trans*-chlorohydrins formed in the TiCl<sub>4</sub>-mediated reactions may arise from a competing pathway in which the chloride is delivered from the opposite face of the C–C double bond in an antiperiplanar fashion. The erosion of *cis* selectivity (1.3:1) in the TiCl<sub>4</sub>-mediated cyclization of **10a** and increased amounts of olefinic products from the cyclization of **10b** may be attributed to the strain and deformation of a bridged cyclic transition state in this bicyclic structure.

The stereoselectivity of the TiCl<sub>4</sub>-mediated cyclization of citronellyl ketone **13** may be rationalized via a chair–chair cyclic transition state (Scheme 2). The mechanism shown should be favored over the alternative path with an equatorially positioned titanate which suffers from apparently more severe 1,3-diaxial CH<sub>3</sub>–H and CH<sub>3</sub>–CH<sub>3</sub> steric interactions.

The *trans* selectivity observed in the HCl-induced cyclizations is consistent with the usual stereoelectronic bias in favor of antiperiplanar transition states for electrophilic additions to C–C double bonds. Moreover, the transition state for the *syn* addition of HCl might be disfavored by the necessary angular distortions from a presumably linear oxygen...H–Cl geometry in the ketone·HCl complex.

The TiCl<sub>4</sub>-mediated Prins cyclization of  $\delta,\epsilon$ - and  $\epsilon,\zeta$ -unsaturated ketones offers a simple stereoselective annulation method for construction of thermodynamically stable, tertiary cyclohexanols with incorporation of a *cis*-chloro substituent. Many questions remain about the scope of nucleophile options, mechanism, and role of the metal ion in this *syn* hydroxyalkylation reaction. The reasons for the predominance of elimination to ene products with alkylaluminum halide reagents<sup>[3]</sup> are unclear. However, this reaction should find application in syntheses of halogenated terpenes<sup>[13]</sup> and various types of functionalized cyclohexanols.

## Experimental Section

**5a**: Representative procedure with TiCl<sub>4</sub> (Table 1, entry 2): The conditions were based on those described in ref. [1a] except that neutralization was done at low temperature. A solution of ketone **4a** (0.80 g, 4.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was stirred and cooled at –78 °C as 1.0 M TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (4.12 mL, 4.12 mmol) was added dropwise over 3 min. After 15 min, a solution of Et<sub>3</sub>N (2.9 mL, 20.6 mmol) and MeOH (0.92 mL, 20.6 mmol) was added dropwise over 2 min. After 5 min at –78 °C, the orange suspension was warmed to RT, diethyl ether (100 mL) was added, and the salts were hydrolyzed by two extractions with 10% HCl (30 mL each). The ethereal solution was washed with saturated NaHCO<sub>3</sub> (30 mL) and saturated NaCl, dried (MgSO<sub>4</sub>) and concentrated by rotary evaporation to give 0.91 g of crude product composed mainly of chlorohydrins **5a** and **6a** (8:1 ratio by <sup>1</sup>H NMR analysis). Purification and separation by flash chromatography on silica gel (98:2 hexane–diethyl ether) gave 0.60 g (63%) of *cis*-chlorohydrin **5a** and 103 mg that was a 5:1 mixture (<sup>1</sup>H NMR analysis) of *trans*-chlorohydrin **6a** (9%) and (1R,6S,9R)-5,5,9-trimethylbicyclo[4.4.0]dec-2(or 3)-en-1-ol (2%) as colorless oils. The major product (**5a**) solidified upon standing; mp 63–65 °C; anal. calcd for C<sub>13</sub>H<sub>25</sub>ClO (230.78): C 67.66, H

10.05, Cl 15.36; found: C 67.74, H 10.35, Cl 15.67. See Supporting Information for IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, COSY, HMQC, HMBC, and NOE data.

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- [10] 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-167996 (**5b**), 167997 (**8b**), and 167998 (**11**). 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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# C–H...O Hydrogen Bond Mediated Chain Reversal in a Peptide Containing a $\gamma$ -Amino Acid Residue, Determined Directly from Powder X-ray Diffraction Data\*\*

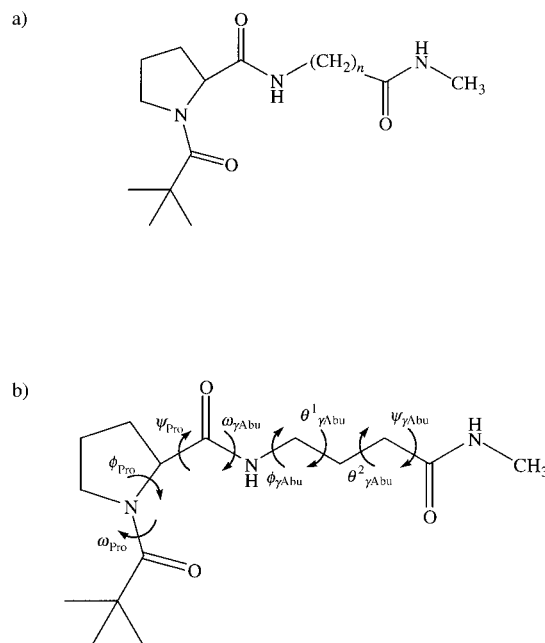
Eugene Y. Cheung, Emma E. McCabe, Kenneth D. M. Harris,\* Roy L. Johnston, Emilio Tedesco, K. Muruga Poopathi Raja, and Padmanabhan Balaram\*

The finding that peptides containing  $\beta$ -amino acid residues give rise to folding patterns hitherto unobserved in  $\alpha$ -amino acid peptides<sup>[1]</sup> has stimulated considerable interest in the conformational properties of peptides built from  $\beta$ ,  $\gamma$ , and  $\delta$  residues,<sup>[2]</sup> as the introduction of additional methylene ( $\text{CH}_2$ ) units into peptide chains provides further degrees of conformational freedom. Studies of the influence of introducing  $\omega$ -amino acids into regular polypeptide structures derived from  $\alpha$  residues have demonstrated that extra methylene groups can be inserted into helical backbones and into the strand and turn segments of  $\beta$  hairpins.<sup>[3]</sup> In regard to the influence of  $\text{CH}_2$  group insertion into the  $i+2$  position of isolated peptide  $\beta$  turns, we are investigating the conformational properties of a series of model sequences Piv-<sup>1</sup>Pro-Xxx-NHMe (defined in Scheme 1 and reference [4]).

The parent peptide Piv-<sup>1</sup>Pro-Gly-NHMe has been shown, through structure determination directly from powder X-ray diffraction data,<sup>[5]</sup> to adopt a classical Type II  $\beta$  turn, previous studies having established the sequence as one that forms a canonical  $\beta$  turn.<sup>[6]</sup> Preliminary CD spectroscopic analysis of the peptides with Xxx =  $\beta$ -Gly,  $\gamma$ -Abu,  $\delta$ -Ava, and  $\epsilon$ -Acp showed that all four peptides give distinctly different spectral bands compared to the parent sequence with Xxx = Gly. Attempts to obtain single crystals of these materials appropriate for single-crystal X-ray diffraction have been unsuccessful, and we have instead exploited the opportunities that now exist for determining crystal structures directly from powder X-ray diffraction data.<sup>[7]</sup> Herein we report the structure of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe determined by ab initio structure solution from powder X-ray diffraction data using the Genetic Algorithm technique<sup>[8]</sup> followed by Rietveld refinement. As discussed below, the structure of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe reveals a novel chain reversal motif that is stabilized by an intramolecular C–H...O interaction.

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Scheme 1. a) Piv-<sup>1</sup>Pro-Xxx-NHMe, where Xxx = -NH-(CH<sub>2</sub>)<sub>n</sub>-CO- ( $n = 1$ , Gly;  $n = 2$ ,  $\beta$ -Gly;  $n = 3$ ,  $\gamma$ -Abu;  $n = 4$ ,  $\delta$ -Ava;  $n = 5$ ,  $\epsilon$ -Acp). b) Definition of the backbone torsional angles in Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe.

Figure 1 (top) shows the molecular conformation of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe in the crystal structure determined from powder X-ray diffraction data. The relevant backbone torsion angles (see references [9] and [3b] for the definition of the

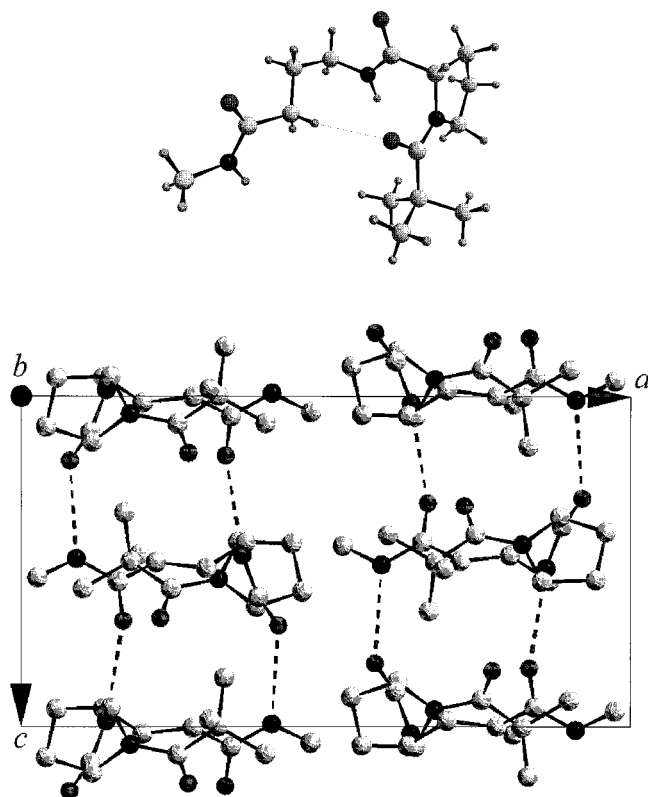


Figure 1. Top: Conformation of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe in the crystal structure. Bottom: Crystal structure of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe illustrating the one-dimensional columns of hydrogen-bonded molecules along the  $c$  axis (hydrogen atoms omitted for clarity).

backbone torsion angles of peptides containing  $\omega$ -amino acids) are:  $\phi_{\text{Pro}} - 71.0$ ,  $\psi_{\text{Pro}} - 26.1$ ,  $\phi_{\gamma\text{Abu}} - 77.2$ ,  $\theta^1_{\gamma\text{Abu}} - 50.2$ ,  $\theta^2_{\gamma\text{Abu}} - 172.2$ , and  $\psi_{\gamma\text{Abu}} + 140.0^\circ$ . The internal torsion angles of the pyrrolidine ring of the Pro residue are:  $\theta$  ( $\text{C}^\delta\text{-N-C}^\alpha\text{-C}^\beta$ )  $- 10.4$ ,  $\chi^1$  ( $\text{N-C}^\alpha\text{-C}^\beta\text{-C}^\gamma$ )  $+ 20.9$ ,  $\chi^2$  ( $\text{C}^\alpha\text{-C}^\beta\text{-C}^\gamma\text{-C}^\delta$ )  $- 23.5$ ,  $\chi^3$  ( $\text{C}^\beta\text{-C}^\gamma\text{-C}^\delta\text{-N}$ )  $+ 17.4$ , and  $\chi^4$  ( $\text{C}^\gamma\text{-C}^\delta\text{-N-C}^\alpha$ )  $- 4.4^\circ$ . The observed conformation is clearly folded, and is reminiscent of chain reversals found in  $\alpha$ -peptide structures. Interestingly, a short  $\text{C-H}\cdots\text{O}$  interaction is observed between one of the  $\alpha$ -methylene hydrogen atoms of  $\gamma$ -Abu and the  $\text{C=O}$  group of Piv. The observed geometry of the hydrogen bond (with the hydrogen atom position normalized according to standard geometries from neutron diffraction) is:  $\text{C}^\alpha\text{-H}_{\gamma\text{Abu}}\cdots\text{O}$  2.51 Å,  $\text{C}^\alpha_{\gamma\text{Abu}}\cdots\text{O}$  3.59 Å,  $\text{C}^\alpha\text{-H}_{\gamma\text{Abu}}\cdots\text{O}$  172.4°. Recently, there has been considerable interest<sup>[10]</sup> in the role of  $\text{C-H}\cdots\text{O}$  interactions in influencing molecular conformation and molecular organization in crystals. The observed geometry of the intramolecular  $\text{C-H}\cdots\text{O}$  interaction in Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe is within the limits generally accepted for significant  $\text{C-H}\cdots\text{O}$  hydrogen bonds.<sup>[10a]</sup> A notable feature of the molecular conformation of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe is that this  $\text{C-H}\cdots\text{O}$  interaction defines an intramolecular cyclic 10-atom motif, similar to that observed in the classical  $\beta$  turn.<sup>[11]</sup> Indeed, the observed motif can be considered as a mimetic of the conformation observed<sup>[5]</sup> in the parent peptide Piv-<sup>1</sup>Pro-Gly-NHMe, with the hydrogen bonding function of the C-terminal amide group now taken by an ethylene moiety. Clearly the formation of the folded structure of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe is facilitated by the *gauche* conformation adopted about the  $\text{C}^\beta\text{-C}^\gamma$  bond of the  $\gamma$ -Abu residue. Indeed, there is growing evidence<sup>[1-3]</sup> that the formation of compact, folded structures by peptides containing  $\beta$ -,  $\gamma$ -, and  $\delta$ -amino acid residues, by adopting *gauche* conformations in polymethylene chains, is fairly widespread. In the cyclic molecular conformation adopted by Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe, all the  $\text{C=O}$  groups point outwards from one face of the molecule and all the  $\text{N-H}$  groups point outwards from the other face, in a manner that is conducive to the formation of columns of hydrogen-bonded molecules along the *c* axis in the crystal (Figure 1 (bottom)). Adjacent molecules along these columns interact through two intermolecular  $\text{N-H}\cdots\text{O}$  hydrogen bonds ( $\text{N-H}(\text{methylamide})\cdots\text{O}=\text{C}(\text{Pro})$ :  $\text{N}\cdots\text{O}$  2.84 Å,  $\text{N-H}\cdots\text{O}$  162.5°;  $\text{N-H}(\gamma\text{-Abu})\cdots\text{O}=\text{C}(\text{methylamide})$ :  $\text{N}\cdots\text{O}$  2.95 Å,  $\text{N-H}\cdots\text{O}$  139.1°).

Our reported *ab initio* structure determination of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe from powder X-ray diffraction data not only reveals a novel structural motif, but in more general terms emphasizes the considerable potential of this approach for revealing structural features of materials that are recalcitrant to the formation of single crystals of suitable size and quality for single-crystal X-ray diffraction studies. Extension of this approach to peptides and other molecular crystals with significantly greater conformational complexity is clearly possible.

### Experimental Section

The synthesis of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe was carried out by coupling Piv-<sup>1</sup>Pro-OH to  $\text{H}_2\text{N}-(\text{CH}_2)_4\text{-COOCH}_3$  using isobutylchloroformate and triethylamine. The isolated dipeptide ester Piv-<sup>1</sup>Pro- $\gamma$ -Abu-OMe was con-

verted into Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe by saturating the methanolic solution with methylamine gas and allowing the mixture to stand at room temperature for 72 h. The peptide was purified by medium pressure liquid chromatography over a reverse-phase  $\text{C}_{18}$  column (40–60  $\mu\text{m}$ ). The structural identity was established by  $^1\text{H}$  NMR spectroscopy (500 MHz) and electrospray mass spectrometry (calcd  $m/z$ : 297 [ $M^+$ ]; found: 298 [ $M+H$ ], 320 [ $M+Na$ ]). The peptide was obtained as a white crystalline solid.

High-quality powder X-ray diffraction data for this sample of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe were recorded at ambient temperature in transmission mode on a Siemens D5000 diffractometer ( $\text{CuK}\alpha_1$  (Ge monochromated); linear position-sensitive detector covering  $8^\circ$  in  $2\theta$ ;  $2\theta$  range:  $5-70^\circ$ ; step size:  $0.019^\circ$ ; data collection time: 10 h).

The unit cell and space group were determined prior to structure solution directly from the powder X-ray diffraction pattern.<sup>[12]</sup> Structure solution from the powder X-ray diffraction data was carried out using our Genetic Algorithm (GA) technique<sup>[8]</sup> within the program EAGER.<sup>[22]</sup> In this method, a population of trial structures is allowed to evolve subject to rules and operations (mating, mutation, and natural selection) analogous to those that govern evolution in biological systems. Each structure is specified by the position  $\{x, y, z\}$ , orientation  $\{\theta, \phi, \psi\}$ , and conformation (defined by variable torsion angles  $\{\tau_1, \tau_2, \dots, \tau_n\}$ ) of each molecule in the asymmetric unit. New structures are generated by the mating and mutation operations, and in the implementation used here,<sup>[8a]</sup> each new structure is subjected to local minimization of the powder profile  $R$  factor  $R_{\text{wp}}$ . In natural selection, only the structures of highest “fitness” (lowest  $R_{\text{wp}}$ ) are allowed to pass from one generation to the next generation. Examples of the application of this method are given in references [5, 8, and 23].

In the structure solution calculation for Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe, the “structural fragment” comprised one complete molecule with hydrogen atoms omitted, and each structure was defined by 13 variables (7 variable torsion angles). The torsion angle ( $\omega_{\text{Pro}}$ ) of the peptide bond of L-proline was restricted to either  $0$  or  $180^\circ$ . The other two amide linkages  $\text{CO-NH}$  were maintained as planar units with a  $\text{O-C-N-H}$  torsion angle fixed at  $180^\circ$ . All other torsion angles were treated as variables. The GA calculation involved the evolution of a population of 100 structures, with convergence on the correct structure solution achieved in 13 generations. 50 mating operations (to produce 100 offspring) and 20 mutation operations were carried out in each generation.

The best structure in the final generation of the GA structure solution calculation was used as the starting model for Rietveld refinement<sup>[24]</sup> (Figure 2), which was carried out using the GSAS program.<sup>[21]</sup> Initially, bond lengths and angles were restrained to standard values and planar restraints were applied to the carbonyl groups. These restraints were gradually relaxed as the refinement progressed. The isotropic displacement parameters of the non-hydrogen atoms were fixed at  $B_{\text{iso}} = 0.05 \text{ \AA}^2$ . Hydrogen atoms were introduced in calculated positions towards the end of the refinement, with  $B_{\text{iso}} = 0.06 \text{ \AA}^2$ . Refinement of a preferred orientation parameter (in the  $[010]$  direction) gave a slight improvement to the

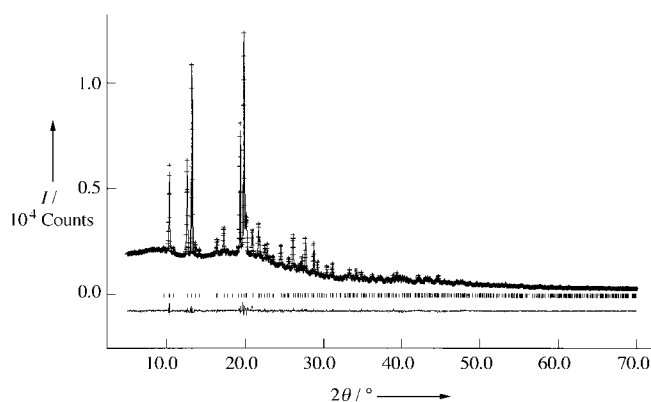


Figure 2. Experimental (+), calculated (solid line), and difference (lower line) powder X-ray diffraction profiles for the Rietveld refinement of Piv-<sup>1</sup>Pro- $\gamma$ -Abu-NHMe. Reflection positions are marked. The calculated powder-diffraction profile is for the final refined crystal structure.

Table 1. Fractional coordinates of Piv-<sup>L</sup>Pro- $\gamma$ -Abu-NHMe.

|     |           |            |           |
|-----|-----------|------------|-----------|
| C1  | 0.0263(6) | 0.721(1)   | 0.548(1)  |
| C3  | 0.1576(4) | 0.6379(6)  | 0.5598(7) |
| C5  | 0.2199(6) | 0.5547(7)  | 0.502(1)  |
| C6  | 0.3019(6) | 0.6098(9)  | 0.519(1)  |
| C7  | 0.3659(6) | 0.5343(7)  | 0.442(1)  |
| C9  | 0.3871(4) | 0.3567(5)  | 0.6077(6) |
| C11 | 0.3839(3) | 0.2173(6)  | 0.6369(5) |
| C12 | 0.4595(4) | 0.1554(8)  | 0.591(1)  |
| C13 | 0.4422(4) | 0.0982(7)  | 0.445(1)  |
| C14 | 0.3540(4) | 0.0801(9)  | 0.440(1)  |
| C16 | 0.2447(3) | 0.1742(6)  | 0.5821(7) |
| C18 | 0.1785(3) | 0.1108(5)  | 0.4982(7) |
| C19 | 0.1929(6) | −0.0291(8) | 0.477(1)  |
| C20 | 0.1011(5) | 0.125(1)   | 0.581(1)  |
| C21 | 0.1683(6) | 0.174(1)   | 0.350(1)  |
| N2  | 0.0902(5) | 0.650(1)   | 0.4903(8) |
| N8  | 0.3612(5) | 0.4027(6)  | 0.480(1)  |
| N15 | 0.3221(3) | 0.1577(7)  | 0.5524(6) |
| O4  | 0.1664(5) | 0.6846(9)  | 0.6784(9) |
| O10 | 0.4204(6) | 0.4230(7)  | 0.6929(9) |
| O17 | 0.2270(4) | 0.2531(8)  | 0.6703(9) |

overall fit. The final refined structure is shown in Figure 1. Fractional atomic coordinates are given in Table 1.

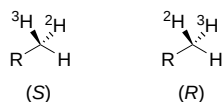
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- [4] Abbreviations used: Piv: Pivaloyl;  $\beta$ -Gly:  $\beta$ -amino propionic acid (also referred to as  $\beta$ -alanine in the early literature);  $\gamma$ -Abu:  $\gamma$ -aminobutyric acid;  $\delta$ -Ava:  $\delta$ -aminovaleric acid;  $\epsilon$ -Acp:  $\epsilon$ -aminocaproic acid.
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- [12] The powder X-ray diffraction pattern was indexed using the programs ITO,<sup>[13]</sup> TREOR,<sup>[14]</sup> DICVOL,<sup>[15]</sup> and GAIN,<sup>[16]</sup> which all gave the following unit cell dimensions with orthorhombic metric symmetry:  $a = 16.96$ ,  $b = 10.77$ ,  $c = 9.15$  Å. Both Pawley fitting<sup>[17]</sup> (using the PowderFit program<sup>[18]</sup> in Materials Studio<sup>[19]</sup>) and LeBail fitting<sup>[20]</sup> (using the GSAS program<sup>[21]</sup>) gave very good fits ( $R_{wp} = 0.018$  and  $R_p = 0.020$ , respectively) to the complete powder diffraction profile using this unit cell. The space group was assigned from systematic absences as  $P2_12_1$ . Density considerations indicate that there is one molecule in the asymmetric unit (with four molecules in the unit cell, the predicted density is  $1.18$  g cm<sup>−3</sup>, consistent with typical densities of organic materials).
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- [24] Summary of final Rietveld refinement:  $a = 16.9433(6)$ ,  $b = 10.7282(3)$ ,  $c = 9.15073(3)$  Å;  $V = 1663.3(1)$  Å<sup>3</sup>;  $R_{wp} = 0.026$ ,  $R_p = 0.019$ ; 64 refined variables, 3397 profile points, 920 reflections;  $2\theta_{max} = 70^\circ$  (1.3-Å resolution).

## The Shortest Route to Chiral Ditosylmethylamine\*\*

Nicolas Faucher, Jean-Christophe Cintrat,\*  
Patrick Berthault, and Bernard Rousseau\*

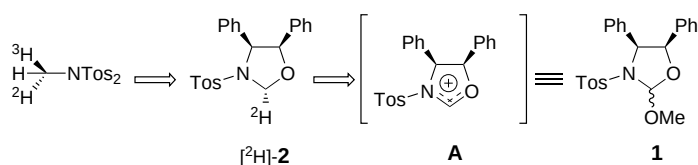
The chiral methyl group (Scheme 1) is an invaluable and unique tool in elucidating biological mechanisms, and has been used to clarify crucial biochemical transformations.<sup>[1–2]</sup> Among the most powerful syntheses of the smallest asymmetric molecule,<sup>[3–5]</sup> the most attractive deal with the preparation of chiral *N,N*-ditosylmethylamine. This synthon is of



Scheme 1. Chiral methyl group.

particular interest since it can be considered to be a bridgehead in obtaining numerous substrates that bear an enantiomerically enriched methyl group by means of a facile  $S_N2$  reaction.<sup>[6]</sup> Although very elegant, Floss's approach, in which chiral acetic acid is converted into the corresponding methylamine by means of a Schmidt degradation, suffers from problems of reproducibility, sometimes resulting in the marked loss of enantiomeric purity of the starting enantiomerically enriched acetic acid.<sup>[7]</sup> Other drawbacks include low overall yield (about 5%) and the number of steps (seven) after the introduction of the radioactive label. Herein we report our preparation of chiral *N,N*-ditosylmethylamine.

We have designed a route based on the following retrosynthetic pathway, which involves two key steps (Scheme 2). The first step takes advantage of orthoamide **1** as a chiral formyl cation equivalent. We assumed that the postulated cationic intermediate **A**, which is obtained from the reaction of **1** with a suitable Lewis acid, could be reduced stereospecifically by a deuteride species to afford  $[^2\text{H}]\text{-2}$ . The second

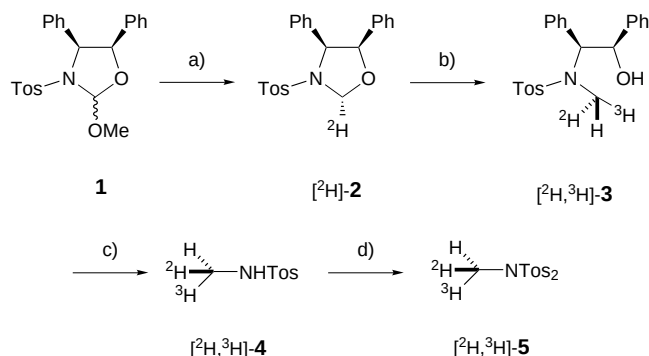


Scheme 2. Retrosynthetic pathway to chiral ditosylmethylamine. Tos = tosyl = *p*-toluenesulfonyl.

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[\*\*] We thank Bruker for the loan of a lockswitch

key step involves the stereocontrolled opening of oxazolidine  $[^2\text{H}]\text{-2}$  with a tritide to yield the chiral methyl group (Scheme 2).



Scheme 3. Synthesis of chiral ditosylmethyl amine. Reagents and conditions: a)  $\text{Bu}_3\text{Sn}^2\text{H}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ ; b)  $\text{Et}_3\text{Si}^3\text{H}$ ,  $\text{TiCl}_4$ ; c)  $\text{HCO}_2\text{NH}_4$ ,  $\text{Pd/C}$  (10%), 66%; d)  $\text{NaH/TosCl}$ , DMF, 80%. DMF = *N,N*-dimethylformamide.

Compound **1** was easily obtained as a mixture of epimeric C2 (d.r. 1:1) through the acid-catalyzed condensation of trimethyl orthoformate with (1*R*,2*S*)-*N*-tosyldiphenylethanolamine (Scheme 3). We have already reported the conversion of **1** into enantiopure  $[^2\text{H}]\text{-2}$  with a combination of  $\text{Bu}_3\text{Sn}^2\text{H}$  and  $\text{BF}_3 \cdot \text{OEt}_2$  to afford  $[^2\text{H}]\text{-2}$  in 82% yield and with an isotopic enrichment higher than 95%.<sup>[8]</sup> Addition of deuteride occurs on the *Re* face of postulated intermediate **A** (anti to the phenyl groups), thus giving (2*R*)- $[^2\text{H}]\text{-2}$  as the sole diastereomer, which was treated with  $\text{Et}_3\text{Si}^3\text{H/TiCl}_4$  to give  $[^2\text{H},^3\text{H}]\text{-3}$ .  $\text{Et}_3\text{Si}^3\text{H}$  was prepared from  $\text{Et}_3\text{SiCl}$  and  $\text{LiAl}^3\text{H}_4$  to reach a specific activity of about  $150 \text{ mCi mmol}^{-1}$ .<sup>[9]</sup> Hydrogenolysis of the chiral auxiliary under heterogeneous catalysis (ammonium formate/Pd) afforded  $[^2\text{H},^3\text{H}]\text{-4}$  in 66% yield. The *N*-tosylmethylamine was further protected with tosyl chloride to afford  $[^2\text{H},^3\text{H}]\text{-5}$  in 80% yield. The enantiomeric purity of  $[^2\text{H},^3\text{H}]\text{-5}$  was analyzed by using the Anet protocol.<sup>[10]</sup> The product  $[^2\text{H},^3\text{H}]\text{-5}$  was therefore submitted to  $S_N2$  reaction with (*R*)-(-)-2-methylpiperidine<sup>[11]</sup> to yield  $[^2\text{H},^3\text{H}]\text{-6}$  (Figure 1), which can be used to determine the enantiomeric purity of the parent compound **5** by means of  $^3\text{H}$  NMR. After dissolution of  $[^2\text{H},^3\text{H}]\text{-6}$  (6 mCi) in  $\text{CD}_2\text{Cl}_2$ , the 640-MHz  $^3\text{H}$  NMR spectrum displayed two well-separated signals (Figure 1). A diastereomeric ratio of 83:17 in favor of (2*R*,7*S*)-**6** was determined by Lorentzian deconvolution and integration of the signals.<sup>[12]</sup> Since the piperidine coupling occurs with inversion of configuration,  $[^2\text{H},^3\text{H}]\text{-5}$  must have the *R* configuration. This major configuration may be attributed to a concerted mechanism during the conversion of **2** into **3** ( $S_N2$  pathway). Unfortunately, the open transition state (*N*-tosyliminium intermediate) also leads to the same stereochemical outcome as assigned using molecular models. Therefore, we can not clearly establish which process governs the stereoselectivity of this reaction. Further experiments are currently in progress to assign the major mechanism of the opening reactions of *N*-tosyl oxazolidines.

In summary, we have described a new synthesis of an enantiomerically enriched methyl group by using only non-enzymatic transformations.<sup>[13]</sup> This simple and reproducible



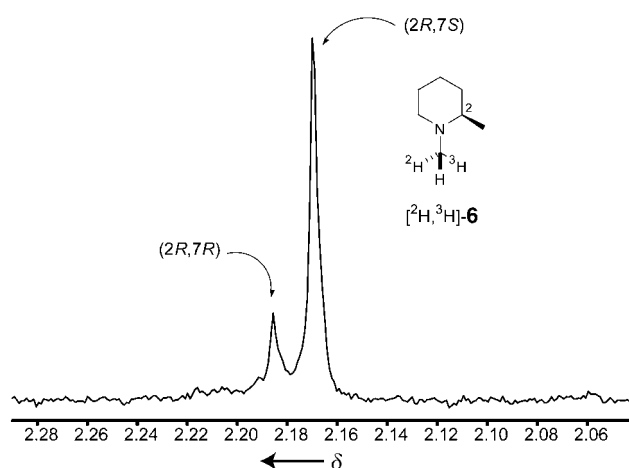


Figure 1.  $^3\text{H}$  NMR spectrum of crude **6** (slow addition of  $\text{TiCl}_4$ ) dissolved in  $\text{CD}_2\text{Cl}_2$  acquired with simultaneous  $^1\text{H}$ - and  $^2\text{H}$ -decoupling (288 K, 640 MHz, 5-kHz spectral width, 2.8-s repetition time).

strategy for the synthesis of chiral *N,N*-ditosylmethylamine is an improvement on the Floss approach:<sup>[7b]</sup> 5 steps compared to 7 in previous reports, and an overall yield of 30%, compared to <5% in the Floss synthesis. Our strategy affords chiral ditosylmethylamine with 66% *ee* (62% for the Schmidt degradation) and can also be used to synthesize the opposite enantiomer starting from commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol.

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- [12] Keeping in mind that upon standing with  $\text{TiCl}_4$  for a few hours, enantiopure  $[\text{H}]\text{-2}$  is prone to epimerization at C2 through an open transition state (*N*-tosyliminium), a slow addition of  $\text{TiCl}_4$  to the mixture of  $[\text{H}]\text{-2}$  and  $\text{Et}_3\text{SiH}$  and careful control of the temperature is mandatory to avoid scrambling of the stereochemistry at the stereogenic methyl center.
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## The Extended Borinium Cation: [(*t*Bu<sub>3</sub>PN)<sub>2</sub>B]<sup>++</sup>

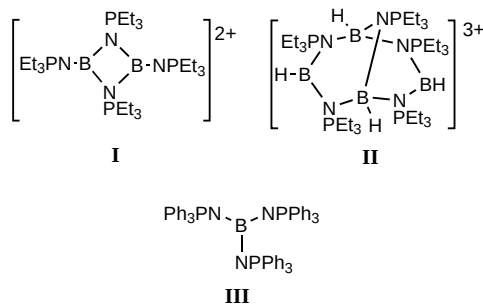
Silke Courtenay, Joshua Y. Mutus, Robert W. Schurko, and Douglas W. Stephan\*

Much of the recent interest in main group metallocenes has arisen from applications as materials precursors for chemical vapor deposition and as activators or catalysts in olefin polymerization. Nonetheless, structure and bonding considerations continue to motivate researchers, as less is known about these main group systems than the transition metal analogues. In this regard, recent studies by Cowley and co-workers, who have described the first examples of decamethylgalloccenium<sup>[1]</sup> and decamethylborococenium cations,<sup>[2]</sup> and by Schnöckel et al, who have reported the decamethylalumococenium cation,<sup>[3]</sup> have begun to redress the balance. Only the Al species displays the symmetric bis- $\eta^5$ -bonded structure analogous to ferrocene. The Ga species exhibits only marginal stability, while the boron compound is described as “tightly squeezed” presumably because of the high effective charge of the boron cation. It is noteworthy that the unsubstituted cyclopentadienyl (Cp) analogues of these cations are not known. In recent work, we employed bulky phosphinimide ligands as steric equivalents to cyclopentadienyl in the development of new active olefin polymerization catalysts.<sup>[4, 5]</sup> Herein, we employ this concept in the formation of a steric

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analogue of borocenium, that is the cation  $[(t\text{Bu}_3\text{PN})_2\text{B}]^+$ . In contrast to previously reported borinium ions,<sup>[6]</sup> this cation has a unique extended structure that contains a linear arrangement of the five atoms of the  $\text{P}=\text{N}-\text{B}-\text{N}=\text{P}$  linkage. This stands in marked contrast to boron derivatives of sterically less demanding phosphinimides for which the dimeric species  $[(\text{Et}_3\text{PN})_2\text{B}]^{2+}$  (**I**),<sup>[7]</sup> the cyclic trications  $[(\text{Et}_3\text{PNBH})_3]^{3+}$ <sup>[8]</sup> and  $[(\text{Et}_3\text{PNBH})_4\text{NPEt}_3]^{3+}$  (**II**),<sup>[9]</sup> or the neutral borane  $(\text{Ph}_3\text{PN})_3\text{B}$  (**III**) have been observed.<sup>[10]</sup>



The lithium salt of tris-*tert*-butylphosphinimide,  $[\text{tBu}_3\text{PN}]\text{Li}$ , reacts with  $\text{BCl}_3$  in refluxing toluene to give a white solid **1** in 72 % yield. The  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum of **1** showed a single resonance signal, while a broad resonance signal was observed in the  $^{11}\text{B}\{^1\text{H}\}$  NMR spectrum. While these data together with the  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra confirmed the formation of a new species **1**, its identity was only established to be  $[(t\text{Bu}_3\text{PN})_2\text{B}]\text{Cl}$  by an X-ray crystallographic study (Figure 1).  $[(t\text{Bu}_3\text{PN})_2\text{B}]\text{Cl}$  (**1**) crystallized in a cubic space group in

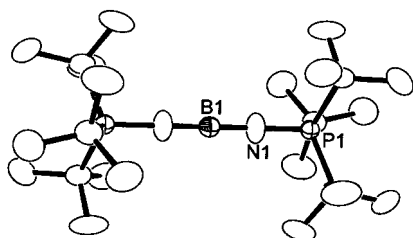
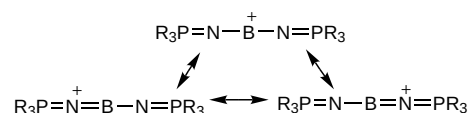


Figure 1. Structure of the cation of **1** (ORTEP drawing, 30 % thermal ellipsoids; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: P1-N1 1.531(5), B1-N1 1.258(5); N1-B1-N1' 180.0(4), B1-N1-P1 180.0(2).

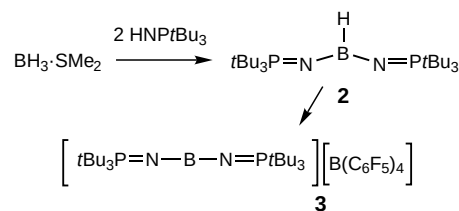
which the  $[(t\text{Bu}_3\text{PN})_2\text{B}]^+$  ion possesses crystallographically imposed  $-3$  symmetry.<sup>[11]</sup> This symmetry requires the B, N, and P atoms sit on the threefold axis of symmetry with the B atom at the center of inversion for the cation. This geometry dictates that both the N-B-N and P-N-B angles are linear. The N-B distance in **1** is 1.258(5) Å, which is thus substantially shorter than the B-N distance of 1.446(8) Å in  $\text{B}(\text{NPPH}_3)_3$ <sup>[10]</sup> or that in the amidoboron cation  $[(\text{Me}_2\text{N})\text{B}(\text{NC}_5\text{H}_6\text{Me}_4)]^+$  (1.30(4), 1.42(4) Å).<sup>[12]</sup> This observation is consistent with both the cationic nature of the B center and B-N multiple-bond character suggested by resonance structures in which the positive charge is distributed onto the N atoms (Scheme 1). The P-N bond length in **1** is 1.531(5) Å, typical of main group



Scheme 1. Resonance structures that are consistent with the cationic nature of the B center and the B-N multiple-bond character.

phosphinimide derivatives.<sup>[13]</sup> The chloride anion sits on a threefold symmetry axis and resides 7.30 Å away from the B center. It is noteworthy that **1** does not react with excess  $[\text{tBu}_3\text{PN}]\text{Li}$ , consistent with the steric demands of these ligands and suggesting an inherent stability of the linear geometry of the five  $\text{P}=\text{N}-\text{B}-\text{N}=\text{P}$  atoms. In contrast, Dehnicke et al. have recently reported that the reaction of excess  $[\text{Ph}_3\text{PN}]\text{Li}$  with  $\text{BF}_3$  affords the species  $\text{B}(\text{NPPH}_3)_3$ .<sup>[10]</sup> Furthermore, in contrast to amidoborinium salts which are formed by abstraction of halide from  $(\text{R}_2\text{N})_2\text{BX}$  by Lewis acids,<sup>[6, 12, 14]</sup> **1** represents the first example in which formation of a borinium cation is spontaneous for a chloride salt. This too reflects the steric demands of the bulky phosphinimide ligands.

The related reaction of two equivalents of  $\text{HNPrBu}_3$  with  $\text{BH}_3\cdot\text{SMe}_2$  proceeds upon refluxing for 1 h to yield, after subsequent work-up, a white powder **2** in 75 % yield (Scheme 2). While NMR data confirmed the formation of a



Scheme 2. Synthesis of **2** and its conversion to **3**.

new species, the data did not define the formulation unambiguously. Recrystallization from toluene/hexanes resulted in isolation of X-ray quality crystals, the subsequent structural determination of which revealed compound **2** to be isomorphous with **1**. However, in the case of **2**, the structural refinement shows a sixfold disorder of a boron atom about the center of the  $-3$  symmetry, thus confirming **2** as  $(t\text{Bu}_3\text{PN})_2\text{BH}$  (Figure 2).<sup>[11]</sup> The N-B-N angle is approximately  $117(2)^\circ$ , while the P-N-B angle is  $148.2(2)^\circ$ .

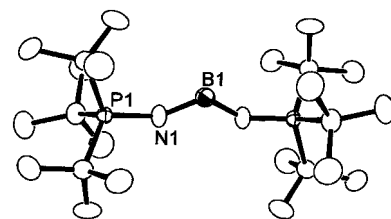


Figure 2. Structure of **2** (ORTEP drawing, 30 % thermal ellipsoids; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: P1-N1 1.535(7), B1-N1 1.41(5); N1-B1-N1'  $117(2)$ , B1-N1-P1  $148.2(16)$ .

Compound **2** reacts with  $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$  resulting in the abstraction of the B-bound hydride affording  $\text{Ph}_3\text{CH}$  and the borinium salt  $[(t\text{Bu}_3\text{PN})_2\text{B}][\text{B}(\text{C}_6\text{F}_5)_4]$  (**3**; Scheme 2). The species **3** was isolated in 65 % yield. This species was also characterized by X-ray crystallography (Figure 3).<sup>[11]</sup> In this

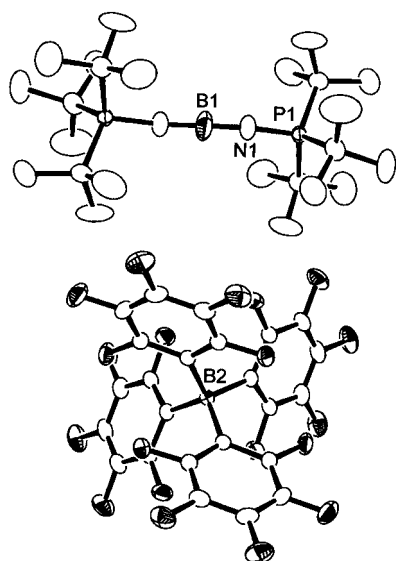


Figure 3. Structure of the cation (top) and anion (bottom) of **3** (ORTEP drawing, 30 % thermal ellipsoids; hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: P1–N1 1.567(3), B1–N1 1.236(3); N1–B1–N1' 180.0(3), B1–N1–P1 162.1(3).

case, only a crystallographic center of symmetry is imposed on the molecule. The geometry at the boron center is linear, while that at the nitrogen centers approaches linearity with a P–N–B angle of 162.1(3)°. The remaining metric parameters of the cation are indistinguishable from those seen in **1** and the geometry of the  $[\text{B}(\text{C}_6\text{F}_5)_4]^-$  ion is typical. The cation–anion separation is indicated by the  $\text{B} \cdots \text{B}$  distance of 10.43 Å.

$^{31}\text{P}\{^1\text{H}\}$  NMR data for **1** show an interesting solvent dependence. In  $\text{CD}_2\text{Cl}_2$  the  $^{31}\text{P}$  NMR resonance signal for **1** was observed at  $\delta = 55.7$ , whereas in  $\text{C}_6\text{D}_6$  the signal appears at  $\delta = 28.5$ . This latter shift is in the range of that seen for **2** ( $\delta = 31.2$ ). In contrast, the  $^{31}\text{P}$  NMR resonance signal for **3** was observed at  $\delta = 55.8$  in either  $\text{CH}_2\text{Cl}_2$  or benzene. It is also noteworthy that addition of  $\text{AlCl}_3$  to a solution of **1** in benzene results in a change in the  $^{31}\text{P}$  NMR chemical shift to  $\delta = 55.8$  consistent with the sequestering of the chloride ion in the  $[\text{AlCl}_4]^-$  ion. These data suggest a tight ion pair of **1** forms in nonpolar solvents, while the ionic form is favored in polar solvents and in the solid state.

Ab initio calculations<sup>[15]</sup> carried out on the model system  $[(\text{H}_3\text{PN})_2\text{B}]^+$  support this view. Full geometry optimization calculations using Gaussian<sup>[16]</sup> B3LYP/6-311G\*\* SCF basis sets<sup>[17, 18]</sup> predict that the boron atom in the  $[(\text{H}_3\text{PN})_2\text{B}]^+$  ion adopts a linear geometry, while in the proximity of chloride ion, the boron becomes trigonal planar with a B–Cl distance of 1.92 Å as expected. This suggests that the linear cationic species **1** is not electronically preferred but is induced by the steric bulk of the phosphinimide ligands. Additional calculations in which the cation of the model  $[(\text{H}_3\text{PN})_2\text{B}]\text{Cl}$  was

constrained to a linear geometry reveal that a tight ion pair with a  $\text{B} \cdots \text{Cl}$  distance of 2.90 Å is 312 kJ mol<sup>−1</sup> more stable than infinitely separated ions. The corresponding NMR shielding calculations (B3LYP/6-311G\*\* GIAO)<sup>[19, 20]</sup> predict that the phosphorus nuclei in the free cation are deshielded by  $\delta = 37.3$  compared to those of the corresponding tight ion pair. These predictions compare with the experimentally observed  $\Delta\delta$  value of 27.2 ppm, which infers that tight-ion pairing occurs for **2** in nonpolar solvents.

## Experimental Section

All preparations were done under an atmosphere of dry,  $\text{O}_2$ -free  $\text{N}_2$  by employing both Schlenk line techniques and an Innovative Technologies or Vacuum Atmospheres inert atmosphere glove box. Solvents were purified by employing a Grubb's type column system manufactured by Innovative Technology. All organic reagents were purified by conventional methods.  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{11}\text{B}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$  NMR spectra were recorded on Bruker Avance-300 and/or -500 spectrometers.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were referenced to  $\text{SiMe}_4$ .  $^{31}\text{P}$  NMR,  $^{11}\text{B}$  NMR, and  $^{19}\text{F}$  NMR spectra were recorded on a Bruker Avance-300 and were referenced to 85 %  $\text{H}_3\text{PO}_4$ ,  $\text{NaBH}_4$  (aq), and  $\text{CFCl}_3$ , respectively. Combustion analyses were performed at Guelph Chemical Laboratories, Guelph, Ontario.

**1**:  $\text{BCl}_3$  (0.224 mmol, 224  $\mu\text{L}$ , 1 M in heptane) was added to a suspension of  $[(t\text{Bu}_3\text{PN})\text{Li}]$  (100 mg, 0.448 mmol) in toluene (10 mL). The resulting white suspension was refluxed overnight, the solvent evaporated, the product dissolved in toluene, and the solution filtered. Compound **1** crystallized in 72 % yield.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta = 1.46$  (d,  $^3J(\text{P,H}) = 14.1$  Hz, 54H);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta = 40.7$  (d,  $^1J(\text{P,C}) = 48$  Hz), 29.3 (s);  $^{31}\text{P}\{^1\text{H}\}$  NMR( $\text{CD}_2\text{Cl}_2$ ):  $\delta = 55.7$ ;  $^{11}\text{B}\{^1\text{H}\}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta = 11.9$  (br);  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 1.35$  (d,  $^3J(\text{P,H}) = 13$  Hz, 54H);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 41.0$  (d,  $^1J(\text{P,C}) = 53$  Hz), 30.2 (s);  $^{31}\text{P}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 28.5$ ;  $^{11}\text{B}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = -6.1$  (br); elemental analysis calcd (%) for  $\text{C}_{24}\text{H}_{54}\text{BClN}_2\text{P}_2$ : C 60.19, H 11.37, N 5.85; found: C 59.66, H 11.80, N 5.47.

**2**:  $\text{BH}_3 \cdot \text{SMe}_2$  (173  $\mu\text{L}$ , 2 M in diethyl ether) was added to a solution of  $\text{HNPrBu}_3$  (150 mg, 0.690 mmol) in toluene (10 mL). The resulting suspension was refluxed for 1 h, cooled to 25 °C, and the solvent removed in vacuo. The product was isolated as a white powder in 75 % yield. Uptake of the powder in a minimum amount of toluene followed by addition of a couple of drops of hexanes resulted in the isolation of X-ray quality crystals.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 1.37$  (d,  $^3J(\text{P,H}) = 12.3$  Hz, 54H);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 40.8$  (d,  $^1J(\text{P,C}) = 50$  Hz), 30.5 (s);  $^{31}\text{P}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 31.2$ ;  $^{11}\text{B}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 24.6$  (br); elemental analysis calcd (%) for  $\text{C}_{24}\text{H}_{55}\text{BN}_2\text{P}_2$ : C 64.86, H 12.47, N 6.30; found: C 64.20, H 12.82, N 5.96.

**3**:  $[\text{Ph}_3\text{C}][\text{B}(\text{C}_6\text{F}_5)_4]$  (664 mg, 0.720 mmol) was added to a solution of **2** (320 mg, 0.720 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL). The solution was stirred overnight, the solvent removed in vacuo, and the resulting white powder washed once with hexanes (1 mL), toluene (1 mL), and hexanes (1 mL). This afforded **3** as a white powder in 65 % yield. Uptake of the powder in a minimum amount of toluene followed by addition of a couple of drops of hexanes resulted in the isolation of X-ray quality crystals.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 1.46$  (d,  $^3J(\text{P,H}) = 14.1$  Hz, 54H);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta = 150.4$ –135.2 (br), 40.8 (d,  $^1J(\text{P,C}) = 48$  Hz), 29.3 (s);  $^{31}\text{P}\{^1\text{H}\}$  NMR( $\text{CD}_2\text{Cl}_2$ ):  $\delta = 55.8$  (s);  $^{11}\text{B}\{^1\text{H}\}$  NMR( $\text{C}_6\text{D}_6$ ):  $\delta = 11.1$  (br),  $-20.8$  (s);  $^{19}\text{F}\{^1\text{H}\}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta = -133.4$  (s),  $-164.1$  (pseudo-t,  $^3J(\text{F,F}) = 18$  Hz),  $-167.9$  (s); elemental analysis calcd (%) for  $\text{C}_{48}\text{H}_{54}\text{B}_2\text{F}_{20}\text{N}_2\text{P}_2$ : C 51.36, H 4.84, N 2.50; found: C 51.62, H 4.94, N 2.33.

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- [11] 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-173106 (**1**), CCDC-173107 (**2**), and CCDC-173108 (**3**). 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). Diffraction experiments were performed on a Siemens SMART System CCD diffractometer and solved by employing the SHELX-TL software package. **1**: Space group:  $P\bar{a}3$ ;  $a = 14.6083(10)$  Å,  $V = 3117.4(4)$  Å<sup>3</sup>,  $Z = 4$ ,  $R = 0.0424$ ,  $R_w = 0.1156$ ,  $GOF = 0.901$ . **2**: Space group:  $P\bar{a}3$ ;  $a = 14.324(6)$  Å,  $V = 2939(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $R = 0.0764$ ,  $R_w = 0.1683$ ,  $GOF = 0.890$ . **3**: Space group:  $P2_1/n$ ;  $a = 11.727(3)$ ,  $b = 8.370(2)$ ,  $c = 27.150(8)$  Å,  $\beta = 97.414(5)^\circ$ ,  $V = 2642.5(13)$  Å<sup>3</sup>,  $Z = 2$ ,  $R = 0.0502$ ,  $R_w = 0.1390$ ,  $GOF = 1.048$ .
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## A Nanoscale Hybrid System Based on Gold Nanoparticles and Heteropolyanions\*\*

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The preparation of hybrid organic–inorganic systems has witnessed major growth in the last few years.<sup>[1]</sup> Increasingly sophisticated nanocomposites with greater added value have been obtained. The interest in such systems lies in the synergy that arises through association of organic and inorganic moieties. An especially interesting class of materials are hybrids based on nanoparticles.<sup>[2]</sup> These are expected to find many applications as sensors or in the fields of magnetism, electronics, and optics. Gold nanoparticles are often involved in the synthesis of nanoscale hybrid systems. An interesting example is the formation of dimer and trimer nanocrystals by exploiting the recognition between oligonucleotide-functionalized Au nanoparticles.<sup>[3]</sup> The stability of such hybrids is strongly related to the irreversibility of the functionalization of the nanoparticles. In the case of Au, Ag, and CdS, alkylthiol groups provide a strong link to the particles.<sup>[3]</sup>

Smaller than gold nanoparticles and intermediate between the colloidal and molecular ranges, the polyoxometalates (POMs) have recently received increasing attention.<sup>[4–8]</sup> Polyoxometalates based on Mo or W constitute a full class of nanobuilding blocks. These metal oxo clusters play a role in many areas.<sup>[4]</sup> Their applications are due to a combination of several valuable properties,<sup>[5]</sup> and to their ability to behave as fully oxidized/(photo)reducible compounds.<sup>[4c]</sup> Their involvement in hybrid organic–inorganic materials is of great interest, and attention was recently paid to the development of ordered assemblies of POMs in such hybrid systems.<sup>[6]</sup> Although numerous studies deal with hybrids including POMs, only a few describe the preparation of hybrids with strong interactions between the organic and inorganic entities. One of these is a hybrid polymer in which organoimido polyoxomolybdates are pendant groups on polystyrene chains.<sup>[7]</sup> Some of us recently described the synthesis of new hybrid networks based on hydrosoluble polymer chains (polyacrylamide) cross-linked by hydrosoluble tetrafunctionalized polyanions.<sup>[8]</sup>

Here we report the synthesis of a new nanoscale hybrid system in which gold nanoparticles (4–12 nm) are associated with the prefunctionalized polyoxometalate  $\gamma$ -[SiW<sub>10</sub>O<sub>36</sub>(RSi)<sub>2</sub>O]<sup>4–</sup> (R = HSC<sub>3</sub>H<sub>6</sub>), designated here as [POM(SH)<sub>2</sub>]<sup>4–</sup>. The organic part R plays two main roles: it forms a covalent link to gold particles through the thiol group

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and a covalent link with the polyanion through the trimethoxysilane group.

The mixing of functionalized nanoparticles and POM is governed by the necessity to avoid reduction of the POM; therefore, it is added in the last step. Hence, a suitable strategy for obtaining POM–Au nanosystems is to synthesize the functionalized POM first, and to adsorb it onto the surface of particles in a second step.<sup>[9]</sup> In the synthesis, the ratio of the concentration of  $[\text{POM}(\text{SH})_2]^{4-}$  to that of  $\text{HAuCl}_4$  was fixed at 1/6. This ratio was chosen to ensure that the surface area of the particles is sufficient to avoid the presence of unadsorbed POM in solution.

$[\text{POM}(\text{SH})_2]^{4-}$  consists of a divalent  $\gamma\text{-}[\text{SiW}_{10}\text{O}_{36}]^{8-}$  polyanion onto which a dimeric siloxane  $\text{RSiOSiR}$  is grafted through four Si–O–W bridges (Figure 1 a). This polyanion was chosen for its easy functionalization with organosilyl groups. Moreover the tetrabutylammonium ( $\text{TBA}^+$ ) counteranion associated with  $[\text{POM}(\text{SH})_2]^{4-}$  provides the POM species with solubility in mixtures such as  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  or  $\text{CH}_3\text{CN}/\text{toluene}$ .

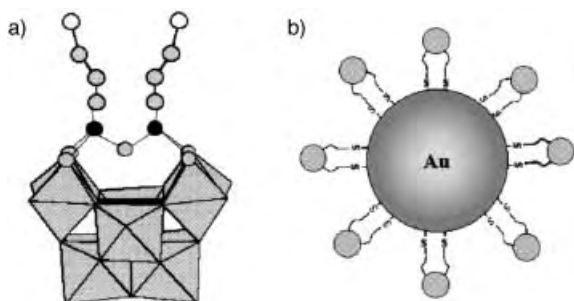


Figure 1. a) Polyhedral representation of the difunctionalized polyanion  $\gamma\text{-}[\text{SiW}_{10}\text{O}_{36}(\text{RSi})_2\text{O}]^{4-}$  ( $\text{R} = \text{HSC}_3\text{H}_6$ ). b) Idealized picture of  $[\text{POM}(\text{SH})_2]^{4-}$  linked through R–S–Au bridges to an Au nanoparticle.

Many studies have been devoted to the preparation of Au nanoparticles, especially by chemical reduction. We used methods described elsewhere<sup>[1, 11]</sup> to obtain particles with average diameters of 4, 8, and 12 nm. In the first method, which leads to large particles, an aqueous solution of  $\text{HAuCl}_4$  was reduced by  $\text{NaBH}_4$  in the presence of trisodium citrate as a stabilizer.<sup>[11]</sup> The hybrid system was then obtained by pouring the aqueous dispersion of gold particles into a solution of  $[\text{POM}(\text{SH})_2]^{4-}$  in acetonitrile. The functionalized gold nanoparticles were recovered as a purple solid and could be dispersed in organic solvents such as acetonitrile, DMF, and DMSO (Figure 2 a).

In the second method, leading to smaller particles,  $\text{HAuCl}_4$  was reduced in toluene with various amounts of tetraoctylammonium bromide ( $\text{NOct}_4\text{Br}$ ). A ratio of  $[\text{NOct}_4]^+ / [\text{AuCl}_4]^-$  of 4.44/1<sup>[2]</sup> leads to particles 4–5 nm in diameter (Figure 2 c). At a lower ratio (1.11/1), the particles were larger (8 nm; Figure 2 b). As in the previous method, a solution of polyanion in acetonitrile was added. The POM-coated particles were then recovered after various treatments and were dispersible in acetonitrile.

The nanohybrids synthesized by these two methods are stable in solution for several months. They were fully characterized by various spectroscopic methods. Powder

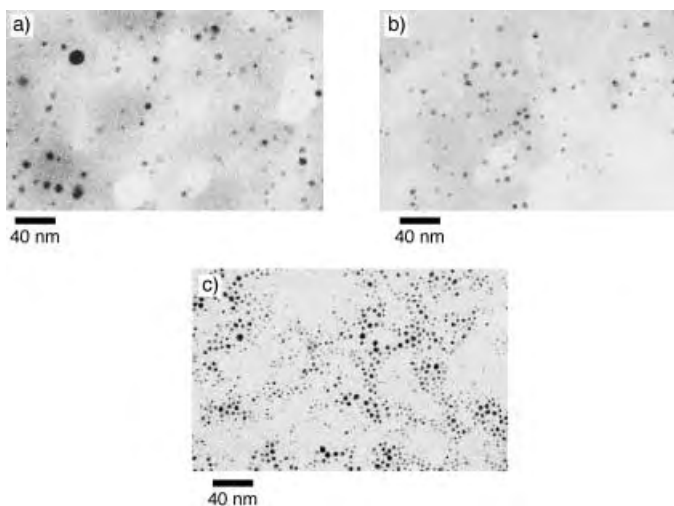


Figure 2. TEM images of hybrid nanoparticles derived from colloidal Au particles of diameter a) 12, b) 8 and c) 4–5 nm.

X-ray diffraction, transmission electron microscopy (TEM), and UV/Vis spectroscopy were used to characterize the Au particles. The powder X-ray diffraction pattern of gold particles obtained from the aqueous solution showed the characteristic 111, 200, 220, 331, 222, and 400 reflections of fcc gold.<sup>[12]</sup> The TEM of hydrosols allowed the particle diameter to be estimated (see Figure 2). The UV/Vis spectra show a broad, particle-size-dependent band which shifts from  $\lambda_{\text{max}} = 520$  (4–5 nm) to  $\lambda_{\text{max}} = 530$  nm (12 nm; Figure 3).

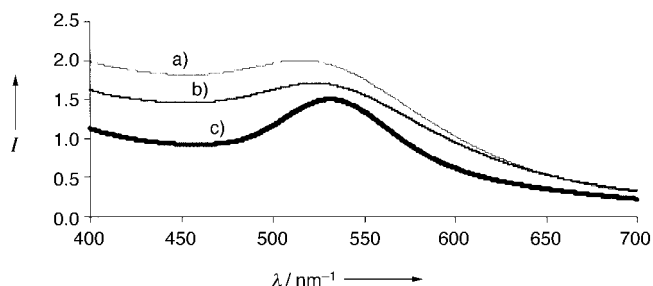


Figure 3. UV/Vis spectra of colloidal solutions of Au nanoparticles of diameter a) 4–5, b) 8, and c) 12 nm.

IR and  $^{183}\text{W}$  NMR spectroscopy were used to characterize the  $[\text{POM}(\text{SH})_2]^{4-}$  moieties. The latter confirmed the presence of POM in the nanosystems: A solution of  $\text{POM}(\text{SH})_2\text{–Au}$  nanoparticles obtained from a hydrosol led to three lines with relative intensity of 2:1:2 (see Supporting Information) and the same chemical shifts as ungrafted  $[\text{POM}(\text{SH})_2]^{4-}$ . These  $^{183}\text{W}$  NMR signals are in good agreement with those of the functionalized POM  $\gamma\text{-}[\text{SiW}_{10}\text{O}_{36}(\text{RSi})_2\text{O}]^{4-}$ .<sup>[10]</sup>

The presence of a covalent link between the two nanobuilding blocks POM and Au was confirmed by IR spectroscopy, in particular by studying of the vibrational band of the thiol groups. For all samples, the IR spectrum shows the same  $\nu_{\text{asym}}(\text{W=O}_{\text{ter}})$  and  $\nu_{\text{asym}}(\text{W–O}_{\text{b}}\text{–W})$  stretching bands as that of the starting polyanionic framework, but it no longer exhibits the characteristic  $\nu_{\text{asym}}(\text{SH})$  band in the region of  $2563\text{ cm}^{-1}$  (Figure 4). This confirms the participation of all the thiol groups in the attachment of POM to gold nanoparticles.

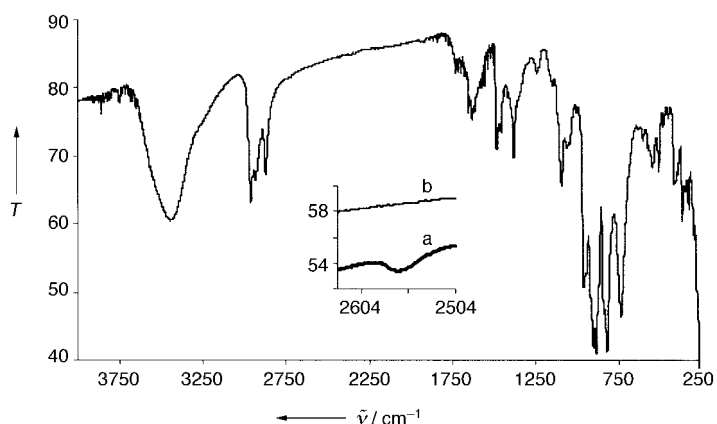


Figure 4. IR spectrum of POM(SH)<sub>2</sub>-Au nanoparticles of 12 nm diameter and abscissa (transmission *T*) expansion of the region of the  $\nu_{\text{asym}}(\text{SH})$  band showing a) the presence of the vibrational band in the starting POM and b) its absence in the hybrid material.

Further evidence for a covalent link between the POM species and the Au nanoparticles through the thiol groups is given by the following experiment: We tried to fix a functionalized polyanion without thiol groups, namely,  $\gamma$ -[SiW<sub>10</sub>O<sub>36</sub>(ClC<sub>3</sub>H<sub>6</sub>Si)<sub>2</sub>O]<sup>4-</sup> ([POM(Cl<sub>2</sub>)]<sup>4-</sup>), solved in acetonitrile, on Au particles synthesized in water. Evaporation of the acetonitrile led to separation of the polyanion and the Au nanoparticles, which were dispersed in aqueous solution. Similar results were obtained with Au particles synthesized in toluene: irreversible aggregation of nanoparticles was observed after the evaporation of toluene, as described by Brust et al.<sup>[13]</sup> The behavior of the product obtained with such polyanions is thus completely different from what is observed with [POM(SH)<sub>2</sub>]<sup>4-</sup>. This confirms the specific ability of the latter to link covalently to Au nanoparticles through its thiol groups.

The attachment of POM on the particles surface results in particular TEM images (see Figure 2). Even when grids contain many particles (Figure 2c) they always seem to be well separated. This could be due to the presence of POM spacers which induce a steric repulsion between the nanoparticles. The TBA<sup>+</sup> counterions associated with [POM(SH)<sub>2</sub>]<sup>4-</sup> remain associated with the POM-Au nanoparticles, and this allows them to be dispersed in organic media.

In contrast to the observations in our previous work on maghemite nanoparticles in coexistence with POM in a hybrid network,<sup>[14]</sup> here we find the [POM(SH)<sub>2</sub>]<sup>4-</sup> directly linked to nanoparticles. To our knowledge, this is the first nanoscale

hybrid system based on Au nanoparticles and POM species with a covalent link between the two nanobuilding blocks (Figure 1b). Thus, it also differs from the Rh nanoparticles functionalized by another POM ([P<sub>2</sub>W<sub>15</sub>Nb<sub>3</sub>O<sub>62</sub>]<sup>9-</sup>) through electrostatic interactions between POM and nanoparticle, described by Finke et al.<sup>[15]</sup> In our case, the (sulfanylpropyl)silyl ligand avoids the desorption of [POM(SH)<sub>2</sub>]<sup>4-</sup> from the particles. Thus, these nanosystems are potentially promising for catalyst applications. Likewise, they can be used as nanobuilding blocks for the realization of hybrid materials because it is also possible to use functionalized counterions of the polyanion. Such a material would have a valuable combination of the properties of both the POM and the Au species.

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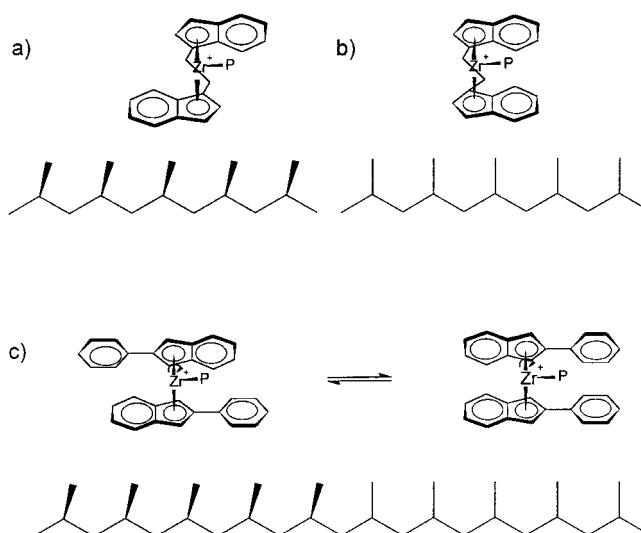
## “Oscillating” Metallocene Catalysts: How Do They Oscillate?\*

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The “metallocene breakthrough”<sup>[1, 2]</sup> has made the dream of tailoring an olefin polymerization catalyst for a desired polymer architecture move closer to reality. In less than one decade since the initial discoveries in the mid-1980s, classes of metallocene catalysts were developed with almost any conceivable kind of stereocontrol (isotactic, syndiotactic, atactic, hemiisotactic), and—most importantly—the relationship was clarified between selectivity on the one hand and symmetry and structure of the catalytic species on the other.<sup>[1, 2]</sup> Therefore, when in 1995 a rational route to isotactic/atactic stereoblock polypropylene (a material of high potential interest for applications as a thermoplastic elastomer<sup>[3]</sup>) was announced,<sup>[4]</sup> the scientific community was—in a way—prepared and there was little room for skepticism.

The idea behind the catalyst design was elegant and conceptually simple (Scheme 1). As is well-known, stereorigid ansa-metallocene catalysts in which two indenyl ligands are locked by a bridge in a *rac*-C<sub>2</sub>-symmetric (Scheme 1a) or a *meso*-C<sub>s</sub> symmetric (Scheme 1b) configuration afford isotactic and atactic polypropylene, respectively.<sup>[1, 2]</sup> The former is a semicrystalline thermoplastic material, with a melting temperature of up to 165 °C; the latter, instead, is uncrystallizable and moderately elastomeric.<sup>[3]</sup> Thus, it was considered worthwhile to try to prepare *unbridged* bis(indenyl) catalysts with substituents of tunable size on the rings, in such a way that hindered ligand rotation is allowed, and a *rac/meso* conformational rearrangement occurs at a rate intermediate between those of monomer insertion and chain growth (transfer).

Support for this strategy was gained from results with [(2-Ar-indenyl)<sub>2</sub>ZrCl<sub>2</sub>] complexes, where Ar is an aryl group which can range from a simple phenyl (**1**; Scheme 1c)<sup>[4]</sup> to much more complicated and bulky moieties, such as 3,5-di-*tert*-butyl-4-methoxyphenyl (**2**).<sup>[5]</sup> Single-crystal X-ray diffrac-



Scheme 1. Mechanistic basis for isotactic/atactic stereoblock propene polymerization with [(2-Ar-indenyl)<sub>2</sub>ZrCl<sub>2</sub>]-based “oscillating” metallocene catalysts (c), according to Coates and Waymouth.<sup>[4]</sup> P = Polymer chain; only C–C bonds traced in the saw-horse chain representations. Stereorigid ansa-metallocene catalysts in which two indenyl ligands are locked by a bridge in a *rac*-C<sub>2</sub>-symmetric (a) or a *meso*-C<sub>s</sub> symmetric (b) configuration afford isotactic and atactic polypropylene, respectively.

tion had proved that complex **1** crystallizes in mixed “*rac*-like” and “*meso*-like” conformations.<sup>[4]</sup> Once combined with suitable cocatalysts,<sup>[1, 2]</sup> it gives rise to a moderately active propene polymerization catalyst.<sup>[4]</sup> Remarkably, the polypropylene produced is largely stereoirregular, but also contains a highly isotactic part;<sup>[4, 5]</sup> the fact that it does perform as a thermoplastic elastomer<sup>[4–6]</sup> was taken as an indication that at least part of the isotactic and stereoirregular sequences are chemically bound, and that therefore crystalline domains act as physical crosslinks between amorphous ones.<sup>[6]</sup> In turn, this was perceived as a validation of the “oscillating” mechanism of Scheme 1c, and the whole class of [(2-Ar-indenyl)<sub>2</sub>ZrCl<sub>2</sub>] catalysts were depicted as clean “molecular switches”.<sup>[4–8]</sup>

On the other hand, a number of facts should have suggested that the reality is somewhat more complicated. In particular:

- 1) Solution NMR investigations on model complexes, down to very low temperatures, did not provide evidence for a slow *rac/meso* interconversion, and only *rac*-like species were detected with certainty.<sup>[9]</sup>
- 2) Computer modeling by means of molecular mechanics, alone<sup>[10]</sup> or combined with quantum mechanics<sup>[11, 12]</sup> confirmed that, for complex **1** and the derived active cation, the *rac*-like and *meso*-like conformations correspond to energy minima, the former being somewhat deeper. However, the activation energy for their interconversion was estimated to be fairly low (2–5 kcal mol<sup>–1</sup>),<sup>[11, 12]</sup> and—at most—comparable with that for monomer insertion (5–15 kcal mol<sup>–1</sup>).<sup>[1]</sup> Considering that the latter is a bimolecular process (hence with a large negative activation entropy), it is difficult to imagine how it can be (much) faster than the intramolecular *rac*-like/*meso*-like rearrangement. Slightly higher interconversion barriers were calculated for complexes with bulkier Ar substituents, such as **2**,<sup>[12]</sup> but in that case the *meso*-like conformation turned

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out to be further disfavored (relative to the *rac*-like one) by steric repulsions between the Ar groups.

- 3) Last but not least, the polymers have broad molecular mass distributions, which is rather unusual with homogeneous catalysts; moreover, they can be solvent-separated in fractions largely differing in stereoregularity, from completely amorphous (though not purely atactic) to highly crystalline (though not completely isotactic).<sup>[2, 5, 6]</sup> Altogether, this strongly suggests the presence of more than one catalytic species, possibly in equilibrium but with average lifetimes longer than the average growth time of individual macromolecules.

Recently, we decided to investigate this complicated subject by means of in-depth microstructural polymer analysis.<sup>[13]</sup> With the aid of advanced high-field (150 MHz) <sup>13</sup>C NMR tools,<sup>[13]</sup> we achieved the first clear-cut microstructural evidence<sup>[14]</sup> that polypropylene samples produced with catalyst systems based on complex **1** can contain a true stereo-block fraction, with fairly long crystallizable isotactic sequences chemically bound to stereoirregular ones.

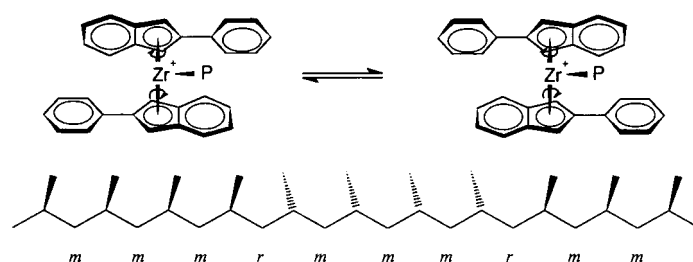
To our surprise, however, we also found that the relative amount of crystallizable blocks is strongly dependent on the cocatalyst and on the solvent. Although appreciable when **1** was activated in toluene with *N,N*-dimethylanilinium tetrakis(perfluorophenyl)borate/[Al(isobutyl)<sub>3</sub>], polymer crystallinity, at least in our hands, dropped practically to zero when methylalumoxane (MAO) in toluene was used, or—irrespective of the cocatalyst—when the polymerization was carried out in a more polar solvent such as 1,2-dichlorobenzene (Table 1, entries 1–5).

This indicates that the active species of **1** is intrinsically much more mobile than has been assumed up to now<sup>[1, 2, 4–8]</sup> and that, at least under certain experimental conditions, ligand rotation takes place at a rate comparable with that of monomer insertion.

Another surprise came from the finding that, in all cases, the stereoirregular part of the polymer is *not* truly

atactic, but rather contains an excess of *meso* (*m*) diads, separated by predominantly isolated *racemo* (*r*) diads (...*mrmrmrmrmrmr*...).<sup>[14]</sup>

Revealingly, the fraction  $P_m$  of *m* diads was found to increase with increasing monomer concentration (Table 1, entries 1–4); this led us to rule out the hypothesis of a weak 1,3-like asymmetric induction<sup>[13, 15]</sup> exerted by the growing chain end when the catalytic species is in the achiral *meso*-like conformation. Instead, we concluded<sup>[14]</sup> that the said microstructure reflects the fact that the *rac*-like conformation is more stable than the *meso*-like one,<sup>[12]</sup> and that—rather (or more) than involving the latter—catalyst “oscillation” mostly occurs *within* the *rac*-like conformation, that is between its two enantiomorphous forms with opposite enantioselectivities (“*rac/rac\** oscillation”, Scheme 2).



Scheme 2. “Oscillation” of a [(2-Ar-indenyl)<sub>2</sub>ZrCl<sub>2</sub>]-based catalyst (shown for Ar = phenyl) between the two enantiomorphous forms of the *rac*-like conformation, and resulting polypropylene microstructure.

Clear evidence in support of the above interpretation now comes from the microstructural characterization of polymers prepared with the slightly “stiffer” catalyst **2**. Figure 1 shows the methyl region of the 150 MHz <sup>13</sup>C NMR spectrum of a typical polypropylene sample obtained with catalyst system **2**/MAO (Table 1, entry 7). The spectrum reveals that the polymer contains isotactic sequences spanned by *isolated r* diads (see, in particular, the intense peak no. 13 of the *mmmrmm* heptad<sup>[13, 16]</sup>), and with just traces of *rr* stereo-defects. Quantitative statistical analysis of polymer configuration<sup>[13]</sup> on the basis of the model of Scheme 2 gives a very good match between experimental and calculated stereo-sequence distributions (see Table S1 in the Supporting Information), with a best-fit value of the *average* stochastic probability of “oscillation”  $P_{osc} \approx (1 - P_m) \approx 0.09$  and an estimated enantioselectivity of the catalytic species of 0.985.

Plausibly, as already observed with catalyst **1**, samples prepared at lower monomer concentration have lower <sup>13</sup>C NMR  $P_m$  (i.e., higher  $P_{osc}$ ) values (Table 1, entries 6 and 7); indeed, decreasing monomer concentration is expected to slow down monomer insertion, but not catalyst oscillation. As an example, the number average length of the isotactic strands with opposite relative configurations (see Scheme 2),  $\langle L_{iso} \rangle \approx (1/P_{osc})$ , turned out to be approximately 5 and approximately 10 monomeric units for samples 6 and 7 of Table 1, respectively.<sup>[17]</sup>

On the other hand, in comparison with **1**, the performance of **2** is less sensitive to the nature of the solvent and/or of the cocatalyst (Table 1, entries 6–9). We will comment on this point later on.

Table 1. Results of propene polymerization in the presence of the “oscillating” metallocene catalysts **1** and **2** (see text).<sup>[a]</sup>

| Entry | Catalyst/<br>Cocatalyst <sup>[b]</sup> | Solvent             | [C <sub>3</sub> H <sub>6</sub> ]<br>[M] | [ <i>mmmmmm</i> ] <sup>[c]</sup><br>[%] | $P_m$ <sup>[d]</sup> | $T_m$ <sup>[g]</sup><br>[°C] | $\Delta H_m$ <sup>[g]</sup><br>[J g <sup>−1</sup> ] |
|-------|----------------------------------------|---------------------|-----------------------------------------|-----------------------------------------|----------------------|------------------------------|-----------------------------------------------------|
| 1     | <b>1</b> /MAO                          | toluene             | 1.5                                     | 5                                       | 0.56 <sup>[e]</sup>  | –                            | Am <sup>[b]</sup>                                   |
| 2     | <b>1</b> /MAO                          | toluene             | 6.7                                     | 8                                       | 0.58 <sup>[e]</sup>  | –                            | Am <sup>[b]</sup>                                   |
| 3     | <b>1</b> /borate/TIBAl                 | toluene             | 1.5                                     | 13                                      | 0.53 <sup>[e]</sup>  | 133                          | 7                                                   |
| 4     | <b>1</b> /borate/TIBAl                 | toluene             | 6.7                                     | 23                                      | 0.59 <sup>[e]</sup>  | 140                          | 10                                                  |
| 5     | <b>1</b> /borate/TIBAl                 | ODCB <sup>[b]</sup> | 1.5                                     | 4                                       | 0.52 <sup>[e]</sup>  | –                            | Am <sup>[b]</sup>                                   |
| 6     | <b>2</b> /MAO                          | toluene             | 1.5                                     | 30                                      | 0.79 <sup>[f]</sup>  | 90                           | 4                                                   |
| 7     | <b>2</b> /MAO                          | toluene             | 6.7                                     | 52                                      | 0.90 <sup>[f]</sup>  | 140                          | 34                                                  |
| 8     | <b>2</b> /borate/TIBAl                 | toluene             | 1.5                                     | 31                                      | 0.76 <sup>[f]</sup>  | 145                          | 9                                                   |
| 9     | <b>2</b> /borate/TIBAl                 | ODCB <sup>[b]</sup> | 1.5                                     | 30                                      | 0.75 <sup>[f]</sup>  | 145                          | 6                                                   |

[a] Experimental conditions:  $T = 20^\circ\text{C}$ ;  $[\text{Zr}] = 3 \times 10^{-5} \text{ M}$ ;  $[\text{Al}]/[\text{Zr}] = 1.0 \times 10^3$  (for activation with MAO);  $[\text{B}]/[\text{Zr}] = 2.5$ ,  $[\text{Al}]/[\text{Zr}] = 3.0 \times 10^2$  (for activation with *N,N*-dimethylanilinium tetrakis(perfluorophenyl)borate/[Al(isobutyl)<sub>3</sub>]); polymerization time, 1.0 h. [b] Abbreviations: borate = *N,N*-dimethylanilinium tetrakis(perfluorophenyl)borate; TIBAl = [Al(isobutyl)<sub>3</sub>]; ODCB = 1,2-dichlorobenzene; Am = Amorphous. [c] <sup>13</sup>C NMR fraction of isotactic heptad in the whole sample. [d] Probability of *m* diad formation, estimated by statistical analysis of the 150 MHz <sup>13</sup>C NMR stereosequence distribution.<sup>[13, 14]</sup> [e] In the stereoirregular sequences. [f] In the whole sample. [g] Measured by differential scanning calorimetry (DSC) on second heating scan.

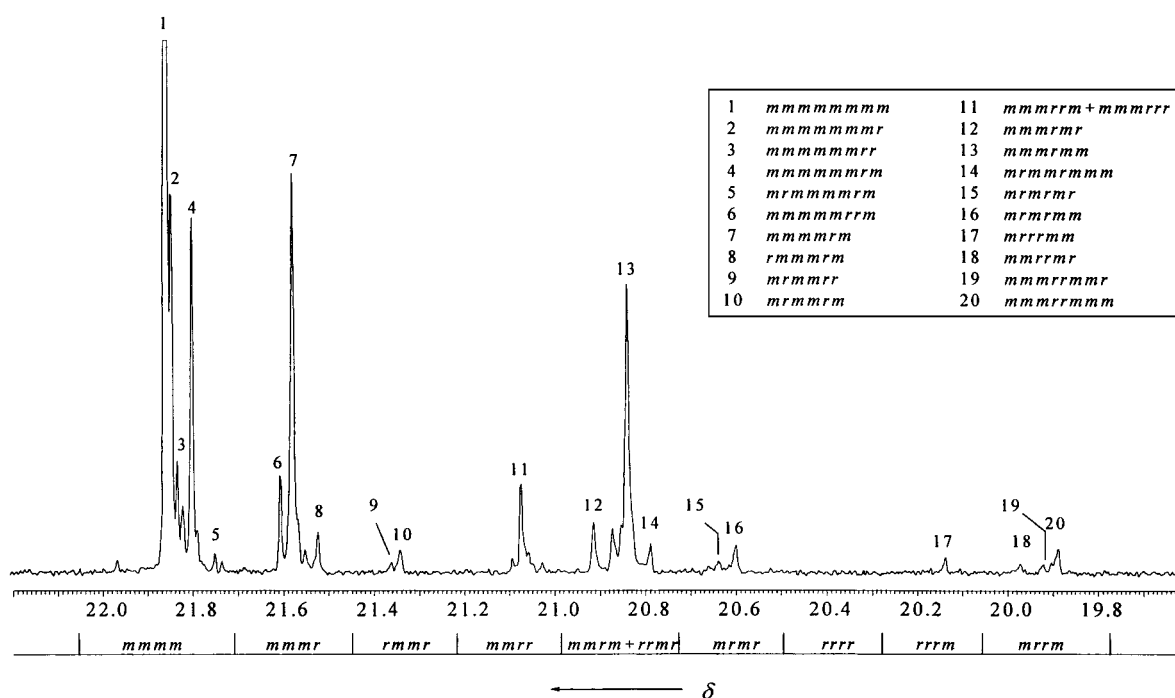


Figure 1. Methyl region of the 150 MHz  $^{13}\text{C}$  NMR spectrum (in 1,2- $[\text{D}_2]$ tetrachloroethane at 90 °C) of a polypropylene sample prepared with catalyst **2** (Table 1, entry 7). The chemical shift scale is referenced to the signal for tetramethylsilane; the assignment is based on references [13, 16]. The presence in the sample of isotactic sequences separated by *single r* diads is apparent (see, in particular, the intense peaks numbered as 4, 7, and 13).

From the results presented so far, one can easily see that (*coeteris paribus*) the ratio between the average frequencies of monomer insertion and catalyst oscillation is critically dependent on the Ar substituent: comparatively high for the bulky catalyst **2**, with  $(1 - P_{\text{osc}})/P_{\text{osc}}$  values of up to approximately 10; fairly low instead for catalyst **1**. For the latter, particularly in a (weakly) polar medium, ligand rotation can be regarded as almost free on the time scale of monomer insertion, with a resulting “quasi-atactic” chain propagation (which obviously implies that some contribution of the *meso*-like form to the catalytic activity<sup>[4–8]</sup> cannot be ruled out). All this fits with the previously discussed results of computer modeling.<sup>[10–12, 18]</sup>

Now we need to explain why, particularly with catalyst **1**, the active species can be frozen *occasionally* in one of the two mirror images of the *rac*-like conformation for a comparatively long time, and thus produce long (well-crystallizable) isotactic blocks. In our opinion, the remarkable cocatalyst and solvent effects documented in Table 1 point to a cation/anion “interlocking” as one of the possible reasons. In this respect, tetrakis(perfluorophenyl)borate, which can establish directional interactions with metallocene cations, seems to be more effective than the large and highly delocalized anion of MAO.<sup>[19, 20]</sup>

The high sensitivity of the stereoselectivity to “environmental factors” is a peculiar and intriguing aspect of this fascinating catalysis. For most stereorigid ansa-metallocene catalysts, and in particular for *rac*- $C_2$ -symmetric ones with homotopic sites, the enantioselectivity is the direct result of the intrinsic ligand structure, and (in spite of the fact that the reaction is normally carried out in a nonpolar medium) the existence of a counterion can practically be ignored as far as

the microstructure of the polymer produced is concerned.<sup>[1, 2, 13]</sup> Only recently have some counterion and solvent effects been documented on the relative rates of monomer insertion and site epimerization (chain back-skip),<sup>[1, 2, 13]</sup> and hence on the syndiotactic selectivity, for  $C_s$ -symmetric ansa-zirconocenes with enantiotopic sites.<sup>[21]</sup> At the other extreme, unbridged achiral bis(cyclopentadienyl) catalysts afford substantially stereoirregular polymers practically under all conditions (apart from a weak chain-end control at very low temperatures in a few cases).<sup>[1, 2, 13]</sup>

Conversely, with their highly mobile but “hooked” ancillary ligands, [(2-Ar-indenyl) $_2\text{ZrCl}_2$ ]-based catalysts can change their stereoselectivity dramatically depending on how they interact with the “outer world”, to the point that they can lose the “single-site” character typical of homogeneous systems.<sup>[1, 2]</sup> As shown in Table 1, a different choice of solvent and/or counterion can affect the dynamics of ligand rotation at least as much as the nature and size of the “built-in” Ar substituents, particularly when the latter are not too bulky and the complex therefore is not too constrained. We will report in more depth on these aspects in the near future.

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## Total Synthesis of the Presumed Amphidinolide A\*\*

Hon Wai Lam and Gerald Pattenden\*

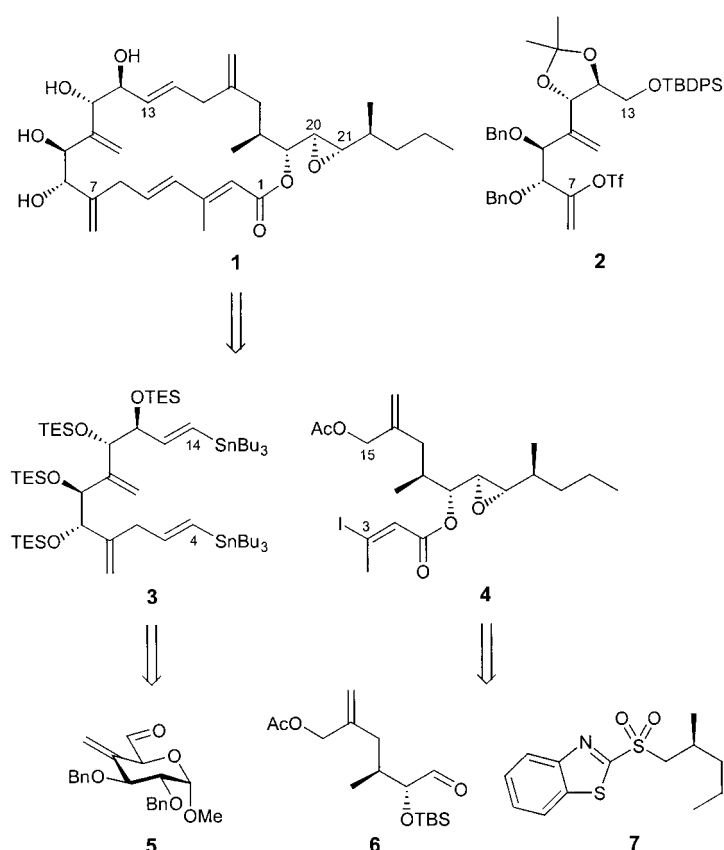
The amphidinolides are a family of biologically active macrolides isolated from the marine dinoflagellate *Amphidinium* sp., which lives in a symbiotic relationship with the Okinawan flatworm *Amphiscolops* sp.<sup>[1]</sup> Many of the amphidinolides show potent cytotoxic activity against murine lymphoma L1210 cells, human epidermoid carcinoma KB cells, and human colon tumor HCT 116 cells.<sup>[1]</sup> Amphidinolide A (**1**) was the first member of the family to be isolated and characterized.<sup>[2]</sup> Its structure incorporates a 20-membered macrolactone that contains six double bonds, three of which are exocyclic. The relative stereochemistry of the nine stereocenters in **1** was suggested by Kobayashi and co-workers on the basis of extensive NMR spectroscopy experiments.<sup>[3]</sup>

Studies towards the synthesis of amphidinolide A (**1**) have been described by O'Connor and Williard,<sup>[4]</sup> by Maleczka and co-workers,<sup>[5]</sup> and by ourselves. In an earlier communication, we described an approach to the macrolactone core of **1** in which a key step involved an intramolecular sp<sup>2</sup>-sp<sup>3</sup> Stille reaction of a precursor that contains an alkenyl stannane and an allylic chloride.<sup>[6]</sup> In subsequent studies, we also described a concise synthesis of the C7–C13 fragment **2**, starting from commercially available methyl- $\alpha$ -D-glucopyranoside.<sup>[7]</sup> Herein we describe a total synthesis of **1**, the proposed structure of amphidinolide A, and also of the diastereomer **34**, which is epimeric to **1** at C20 and C21.

Our synthetic strategy to amphidinolide A (**1**) required the preparation of two major fragments **3** and **4**, which we planned to elaborate into **1** through the following sequence of operations: 1) an intermolecular sp<sup>2</sup>-sp<sup>2</sup> Stille reaction<sup>[8]</sup> between the less sterically hindered C4 alkenyl stannane unit in **3** and the C3 alkenyl iodide of **4**; 2) deprotection of all the silyl ethers originally in **3**; and 3) an intramolecular sp<sup>2</sup>-sp<sup>3</sup> Stille reaction<sup>[9]</sup> between the C14 alkenyl stannane and the C15 allylic acetate (Scheme 1). The intermolecular Stille reaction of **3** with **4** was deemed to be highly challenging, as it requires not only the discrimination between the two alkenyl stannane units in **3**, but also between the alkenyl iodide and the allylic acetate units in **4**, both of which are potentially reactive under palladium-catalyzed coupling conditions. However, the observation that sterically encumbered alkenyl stannanes are often poor substrates in the Stille reaction,<sup>[10]</sup> together with our expectation that an alkenyl iodide would be more reactive than an allylic acetate, led us to believe that the reaction could be selective. We planned to prepare the bis-alkenyl stannane **3** from the known aldehyde **5**,<sup>[7]</sup> and to prepare the iodide acetate **4** by using a modified Julia olefination reaction<sup>[11]</sup> between aldehyde **6** and benzothiazolyl sulfone **7** as a key step.

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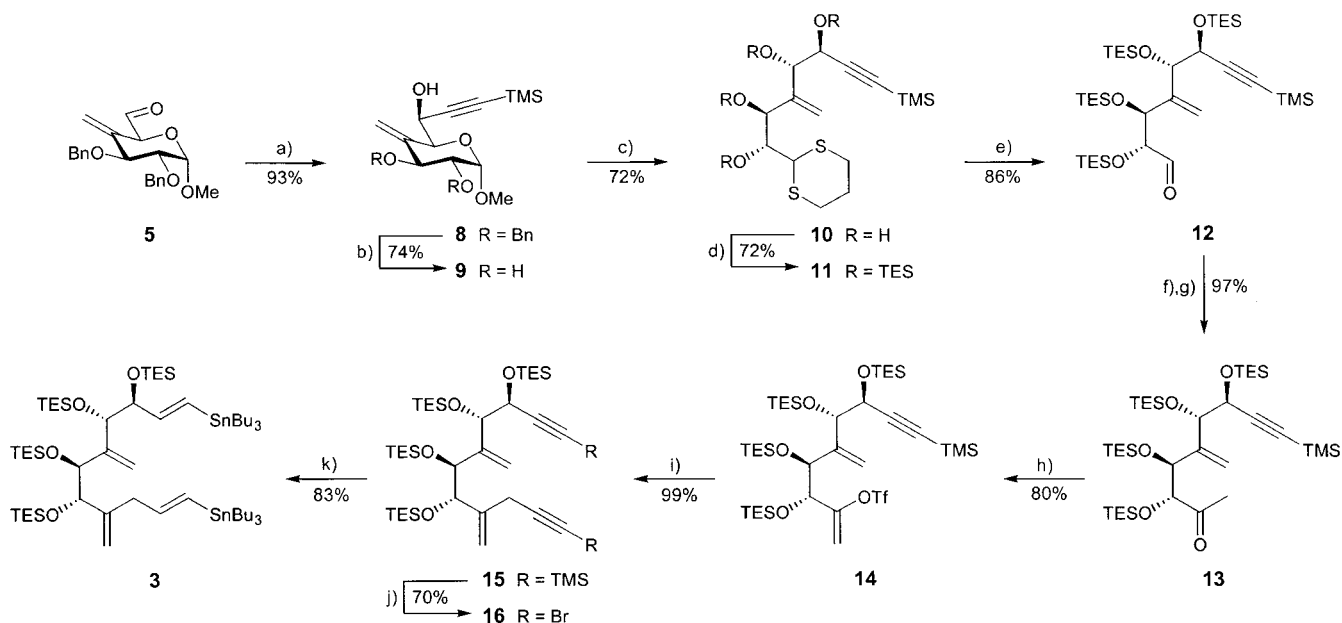
Scheme 1. Retrosynthetic analysis of **1**, the proposed structure of amphidinolide A

Thus, the chelation-controlled addition of trimethylsilyl-ethynylmagnesium bromide to aldehyde **5** first gave alcohol **8**, which was isolated as a single diastereomer in 93% yield

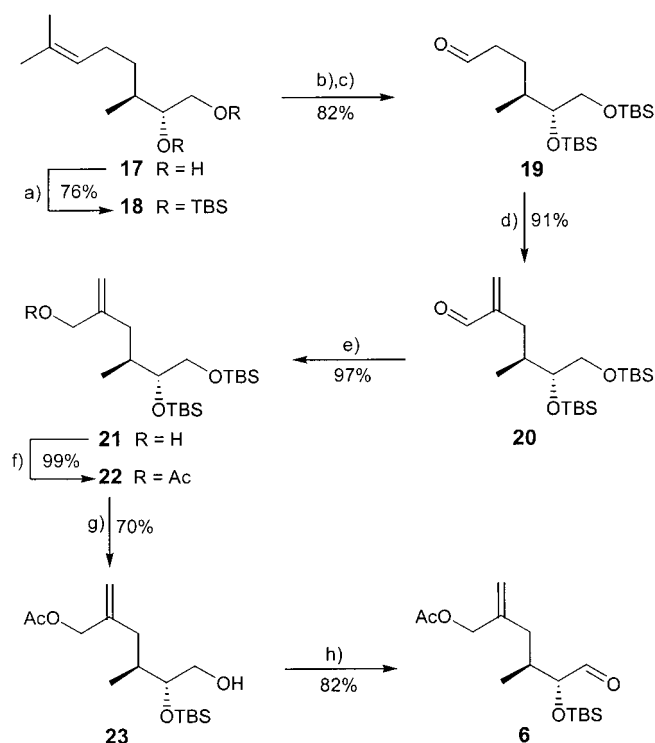
(Scheme 2).<sup>[12, 13]</sup> Debenzylation of **8** by using DDQ,<sup>[14]</sup> followed by a thioacetalization/ring-opening reaction of the resulting cyclic acetal **9** with propane-1,3-dithiol next led to the acyclic tetraol **10**. After silylation of the hydroxy groups in **10**, the thioacetal group in the product **11** was removed by using NBS in aqueous acetone<sup>[15]</sup> to reveal aldehyde **12**. A straightforward homologation of **12** to the corresponding methyl ketone **13** was followed by the formation of alkenyl triflate **14**, which upon reaction with the Gilman reagent derived from (3-trimethylsilylprop-2-ynyl)lithium and copper(I) iodide, gave the bis-TMS-alkyne **15** in excellent yield. After exchanging the alkyne TMS protecting groups in **15** for bromides by the action of NBS and AgNO<sub>3</sub>,<sup>[16]</sup> palladium-catalyzed hydrostannylation<sup>[17]</sup> of the resulting bis-bromoalkyne **16** finally gave (*E,E*)-bis-alkenyl stannane **3** in 83% yield.

Aldehyde **6**, which is required for elaboration into **4**, was synthesized as shown in Scheme 3 starting from the previously described diol **17**.<sup>[18]</sup> Thus, protection of **17** as its bis-TBS ether **18**, followed by oxidative cleavage of the alkene gave aldehyde **19**. Reaction of **19** with Eschenmoser's salt<sup>[19]</sup> next gave  $\alpha,\beta$ -unsaturated aldehyde **20**, which upon reduction under Luche conditions followed by acetylation of the resulting allylic alcohol **21** gave **22**. The primary TBS ether group in **22** was removed selectively by using CSA, thus leading to alcohol **23**, along with 12% of recovered **22**, which could be recycled. Finally, oxidation of **23** with TPAP/NMO,<sup>[20]</sup> gave aldehyde **6**.

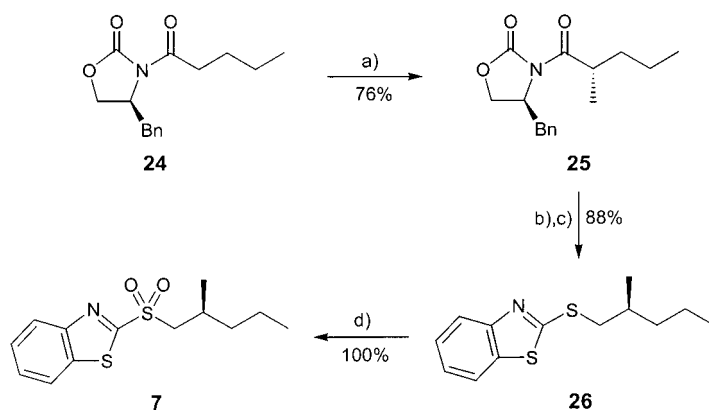
The chiral benzothiazolyl sulfone **7**, which is required for coupling to aldehyde **6**, was prepared from the known acylated oxazolidinone **24**<sup>[21]</sup> (Scheme 4). Methylation of the sodium enolate derived from **24** proceeded with 91:9 diastereoselectivity and gave, after purification, the diastereomerically pure alkylated product **25** in 76% yield.<sup>[22]</sup> Reductive



Scheme 2. Reagents and conditions: a) (trimethylsilyl)acetylene, *n*BuLi, Et<sub>2</sub>O, 0 °C → RT, 15 min, then MgBr<sub>2</sub>, RT, 15 min, then **5**, MgBr<sub>2</sub>, −30 °C → RT, 1 h; b) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (19:1), Δ, 24 h; c) propane-1,3-dithiol, BF<sub>3</sub> · OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h; d) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 5 h; e) NBS, 2,6-lutidine, acetone/H<sub>2</sub>O (9:1), RT, 40 min; f) MeMgBr, CH<sub>2</sub>Cl<sub>2</sub>, −78 °C, 15 min; g) Dess–Martin periodinane, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 35 min; h) KHMDS, PhNTf<sub>2</sub>, THF, −78 → 0 °C, 3 h; i) LiCu(CH<sub>2</sub>C≡TMS)<sub>2</sub>, THF, −20 °C → RT, 12 h; j) NBS, AgNO<sub>3</sub>, acetone, RT, 10 h; k) Bu<sub>3</sub>SnH, Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, RT, 4 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TESOTf = triethylsilyl trifluoromethanesulfonate, NBS = *N*-bromosuccinimide, HMDS = bis(trimethylsilyl)-amide.



Scheme 3. Reagents and conditions: a) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT, 12 h; b) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O (10:1), RT, 3 d; c) NaIO<sub>4</sub>/SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 3 h; d) CH<sub>2</sub>=NMe<sub>2</sub><sup>+</sup>I<sup>-</sup>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT, 12 h; e) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 0 °C, 30 min; f) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, RT, 3 h; g) CSA, MeOH, 0 °C, 3.5 h; h) TPAP, NMO, 4-Å molecular sieves, CH<sub>2</sub>Cl<sub>2</sub>, RT, 1 h. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, NMO = 4-methylmorpholine-*N*-oxide, DMAP = 4-dimethylaminopyridine, CSA = camphorsulfonic acid, TPAP = tetrapropylammonium perruthenate.

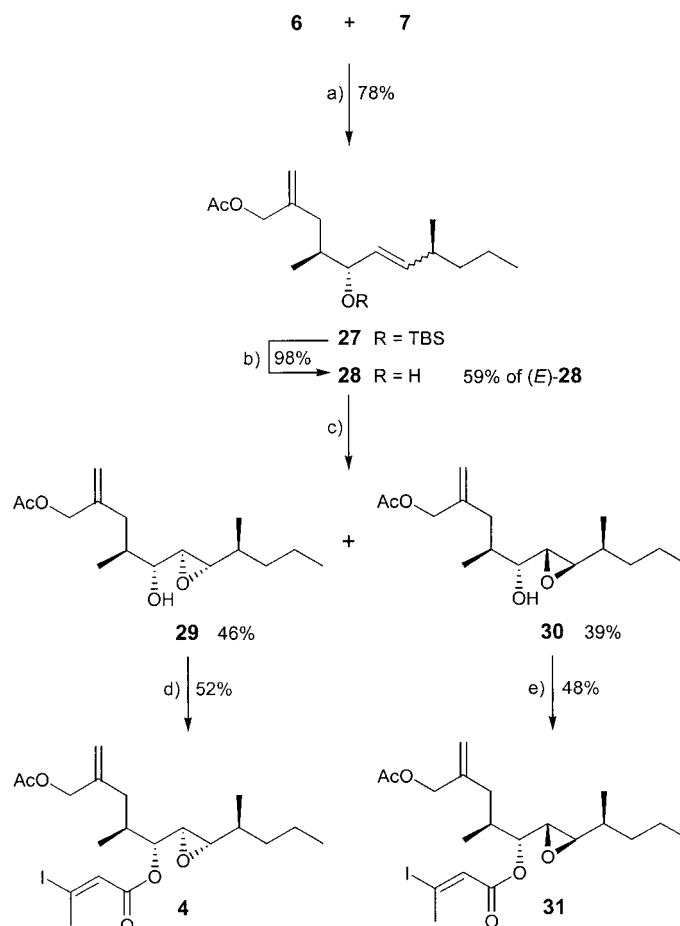


Scheme 4. Reagents and conditions: a) NaHMDS, MeI, THF, -78 °C → RT, 5 h; b) LiBH<sub>4</sub>, MeOH, Et<sub>2</sub>O, 0 °C, 3 h; c) 2-mercaptobenzothiazole, DEAD, PPh<sub>3</sub>, THF, RT, 12 h; d) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, RT, 4 h. DEAD = diethyl azodicarboxylate, *m*CPBA = 3-chloroperbenzoic acid.

removal of the chiral auxiliary in **25**, followed by a Mitsunobu reaction of the resulting crude alcohol with 2-mercaptobenzothiazole gave sulfide **26** in 88 % yield over two steps. Oxidation of **26** with *m*CPBA finally gave the sulfone **7** in virtually quantitative yield.

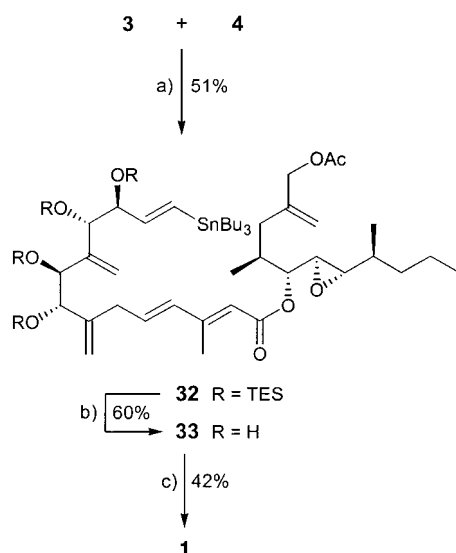
A one-pot Julia reaction<sup>[11]</sup> between **6** and **7**, using KHMDS in THF, led to alkene **27** as an inseparable mixture of *E* and *Z*

isomers (4:1; Scheme 5). Removal of the TBS ether group in **27** with HF·pyridine allowed the isolation of pure allylic alcohol (*E*)-**28**, which was epoxidized by using *t*BuOOH and Ti(O*i*Pr)<sub>4</sub> to give the diastereomeric epoxides **29** and **30**. Epoxy alcohol **29**, which is required for the synthesis of **1** was used to esterify (*E*)-iodobut-2-enoic acid,<sup>[23]</sup> leading to **4**. Similarly, diastereomer **30** was converted into **31**.



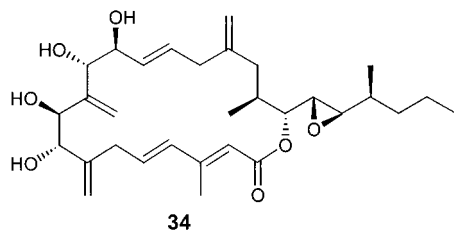
Scheme 5. Reagents and conditions: a) **7**, KHMDS, THF, -78 °C, 30 min, then **6**, -78 °C → RT, 3 h 45 min; b) HF·pyridine, 2,6-lutidine, THF, RT, 15 h; c) *t*BuOOH, Ti(O*i*Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 6 h; d) (*E*)-3-Iodobut-2-enoic acid, DIC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 6 h; e) (*E*)-3-Iodobut-2-enoic acid, EDC, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 12 h. DIC = 1,3-diisopropylcarbodiimide, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

With both key fragments **3** and **4** in hand, a novel selective intermolecular sp<sup>2</sup>-sp<sup>2</sup> Stille reaction that entails the use of Farina's catalyst combination<sup>[24]</sup> in refluxing THF gave diene (*E,E*)-**32**, which was isolated in 51 % yield (Scheme 6). The alkenyl stannane unit in **32** was rendered more reactive to the final sp<sup>2</sup>-sp<sup>3</sup> Stille macrocyclization by deprotection of its TES ethers with PPTS, to give tetraol **33**. Finally, an sp<sup>2</sup>-sp<sup>3</sup> Stille macrocyclization of **33** by using Farina's catalyst in the presence of lithium chloride in cyclohexane gave the polyene polyol macrolide **1** in an unoptimized 42 % yield. To the best of our knowledge, this macrocyclization represents the first example of an intramolecular sp<sup>2</sup>-sp<sup>3</sup> Stille reaction between an alkenyl stannane and an allylic acetate.<sup>[25]</sup>



Scheme 6. Reagents and conditions: a)  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Ph}_3\text{As}$ , THF, 60 °C, 4 h; b) PPTS, MeOH,  $\text{CH}_2\text{Cl}_2$ , RT, 6 h; c)  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Ph}_3\text{As}$ , LiCl, cyclohexane,  $\Delta$ , 3 h. dba = dibenzylideneacetone, PPTS = pyridinium *p*-toluenesulfonate.

Comparison of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data of **1** with those reported for amphidinolide A<sup>[3]</sup> revealed that they were not identical, and showed that we had, in fact, prepared a diastereomer of the natural product. The NMR spectroscopic data of synthetic **1** are fully consistent with the structure proposed for amphidinolide A,<sup>[2]</sup> and assignments for **1** were made on the basis of a combination of chemical shift and coupling constant data, along with HMQC and HMBC spectral data. However, there are significant discrepancies in the chemical shift values compared to those reported for the natural product. Kobayashi and co-workers proposed the relative stereochemistry of amphidinolide A purely on the basis of NOESY data.<sup>[3]</sup> Since the interpretation of the relative configuration of stereogenic centers in macrocyclic compounds by spectral means is not trivial, their assignment was only tentative, and it seems likely that the actual structure of amphidinolide A is epimeric to the proposed structure **1** at one or more stereocenters. It would appear therefore, that a revision of the stereochemistry of the natural product is required. Similarly, **31** was subjected to the identical sequence of reactions depicted in Scheme 6 to give **34**, the C20, C21 bis-epimer of **1**, which was also shown to be a diastereomer of the natural product.



In conclusion, we have synthesized **1**, which has the proposed structure of amphidinolide A, along with a diastereomer **34**. The synthesis proceeded in 21 steps for the longest

linear sequence, starting from methyl- $\alpha$ -D-glucopyranoside, and relied heavily on the judicious use of both inter- and intramolecular Stille reactions for key bond constructions.

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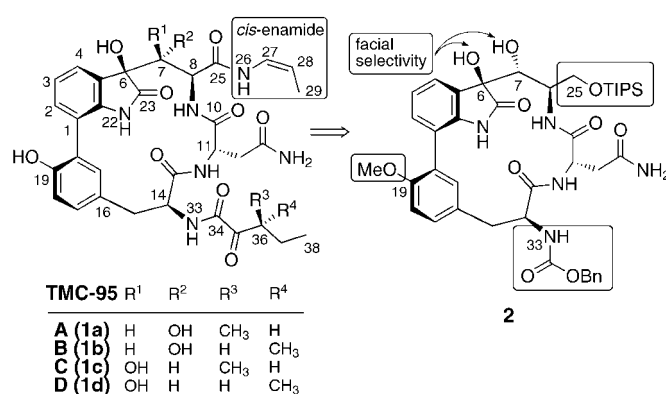
# The Total Synthesis of Proteasome Inhibitors TMC-95A and TMC-95B: Discovery of a New Method To Generate *cis*-Propenyl Amides\*\*

Songnian Lin and Samuel J. Danishefsky\*

The ubiquitin proteasome pathway is critical for accomplishing proteolysis in both the cytosol and nucleus of all eukaryotic cells.<sup>[1]</sup> Understanding of the physiological roles of a particular proteasome has been aided by studying the effects of cell-permeable inhibitors. Moreover, specific proteasome inhibitors are emerging as possible drug candidates.<sup>[1c]</sup> Accordingly, the discovery of the cyclic peptides TMC-95A–D (**1a–d**; see Scheme 1), first isolated as fermentation products of *Apoispora montagnei* SACC TC 1093 derived from soil samples,<sup>[2]</sup> was of great interest.<sup>[3,4]</sup> The A and B isomers of **1**, which differ in stereochemistry at the remote, configuratively labile C36 center, inhibit proteasomal functions of the 20S proteasome with IC<sub>50</sub> values down to low nanomolar levels.<sup>[2a]</sup>

Accordingly, a total synthesis program, which targets the more active TMC-95A and B isomers, was launched in our laboratory. We hoped to gain access to both compounds since after a successful total synthesis the groundwork would be more promising for establishing systematic SAR profiles of these TMC-95 inhibitors. Ideally, simpler structures could be designed, synthesized, and screened for similar activity in anticipation of their use as new drug leads.

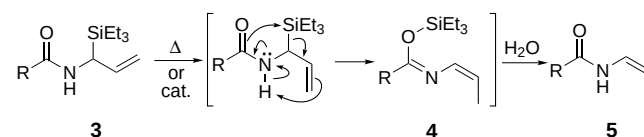
Recently, we described an approach to accomplish stage I in our program, that is, the total synthesis of the TMC-95 inhibitors.<sup>[4a]</sup> The most advanced structure reported in our previous disclosure was compound **2** (Scheme 1). The attainment of this subgoal, promising as it was for our proposed program, still left unaddressed several key issues for total syntheses of **1a** and **1b**. Thus, provision would be necessary to allow exposure of a free phenolic hydroxy group at C19 and a homopyruvoyl group at N33 (see structure **2**). Moreover, the oxidation level at C25 must be upgraded from an alcohol, as found in **2**, to the carboxy state required to reach **1** (see below). This was no trivial matter, given the free hydroxy groups at C6 and C7 in our model target, **2**. We also note that in the synthesis of **2** the facial sense of *cis* dihydroxylation at



Scheme 1. Structures of TMC-95A–D (**1a–d**) and **2**. TIPS = triisopropylsilyl, Bn = benzyl.

C6 and C7 was virtually stereorandom.<sup>[4a]</sup> Perhaps most problematic was the *cis*-propenyl amide linkage that encompasses atoms N26–C29 of the multifaceted molecular ensemble of **1**. It is with this latter issue that we commence our report.

Examination of the literature reveals several methods that might, in principle, be relevant to the enamide problem.<sup>[5]</sup> However, the applicability of these methods to the synthesis of the active TMC compounds is not certain. Compounds **1** have a rich diversity of functionality, particularly in the extended “pyruvoyl”-like (C34–C38) and dihydroxyindolinone (positions 22, 23, and 6–8) regions. Anticipation of potential vulnerability in these sectors, not to speak of the *cis*-enamide itself (N26–C29), prompted us to explore a new modality for reaching such a substructure appropriate for molecules with multiple sites of potential instability. We wondered whether a substance of the type **3** might, upon heating or catalysis, undergo concurrent ene- and silatropic-like bond reorganizations that would lead to **4** (Scheme 2). If this hypothesis were to be fruitful, the *cis* character of the enamide would be virtually assured at the kinetic level. Moreover, it seemed at least possible that the intermediate silyl imidate linkage in **4** could be cleaved, with retrieval of general substructure **5**.



Scheme 2. Formation of *cis*-propenyl amides **5** by rearrangement–hydrolysis of  $\alpha$ -silylallyl amides **3** (R = aryl, alkenyl, and alkyl groups).

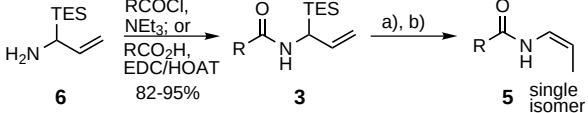
In the event, a range of probe substrates **3** was synthesized by acylation of the known of amine **6** (Table 1).<sup>[6]</sup> As seen in entries 1–3, heating of these compounds at about 110 °C for the time periods indicated gave rise to silyl imidates **4a–c** (observed by <sup>1</sup>H NMR analysis).<sup>[7]</sup> Aqueous hydrolysis of these compounds afforded enamides **5a–c**. The reaction was also applicable to substrate **3d** (entry 4), though a longer heating time was required for its conversion to **4d**. Most significantly, the rearrangement–hydrolysis sequence proved extendable to the aminoacyl substrate **3e** (entry 5) to afford

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Table 1. Rearrangement–hydrolysis of  $\alpha$ -silylallyl amides **3**.<sup>[a]</sup>

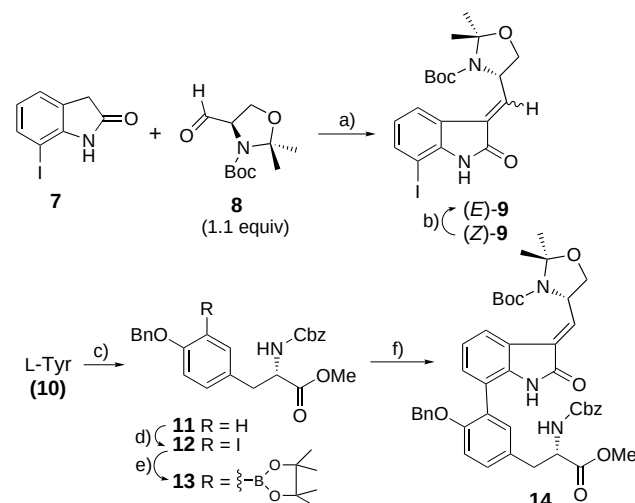


| Entry | R = | Conditions                                            | Yield [%] |
|-------|-----|-------------------------------------------------------|-----------|
| 1     |     | a) toluene, 110 °C, 10 h; b) H <sub>2</sub> O         | 81        |
| 2     |     | a) toluene, 110 °C, 20 h; b) H <sub>2</sub> O         | 73        |
| 3     |     | a) toluene, 110 °C, 27 h; b) H <sub>2</sub> O         | 67        |
| 4     |     | a) toluene, 110 °C, 3 d; b) H <sub>2</sub> O          | 72        |
| 5     |     | a) <i>o</i> -xylene, 135 °C, 4 d; b) H <sub>2</sub> O | 52        |

[a] TES = triethylsilyl, Boc = *tert*-butoxycarbonyl, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, HOAT = 1-hydroxy-7-azabenzotriazole.

**4e** and thence **5e**. It was of great interest to determine whether this new method would find application at a very late stage of our projected total synthesis.

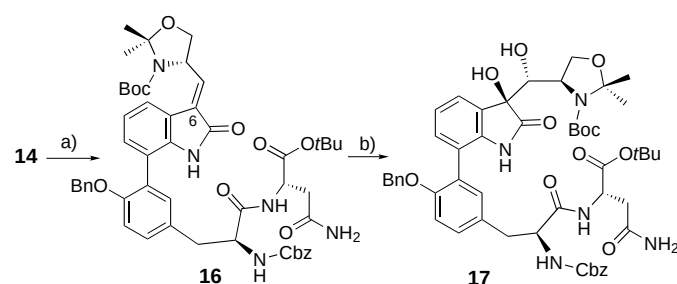
The starting material for our refashioned synthesis was the previously described iodooxindole **7** (Scheme 3).<sup>[4a]</sup> Crossed-aldol condensation of **7** with the Garner aldehyde **8**,<sup>[8]</sup> followed by  $\beta$ -elimination of the derived mesylate, afforded



Scheme 3. Synthesis of biaryl compound **14**. a) LDA (2.0 equiv), THF, –78 °C, 1.5 h; NEt<sub>3</sub>, MsCl, CH<sub>2</sub>Cl<sub>2</sub>, –70 → –50 °C, 1.5 h; 81 % (*E/Z* = 1.3:1); b) I<sub>2</sub> (cat.), benzene, 80 °C, 26 h; DMP/PPTS, toluene, 65 °C, 5 h; 85 % (60 % conversion); c) 1) MeOH/SOCl<sub>2</sub>; 2) CbzCl/K<sub>2</sub>CO<sub>3</sub>; 3) BnBr, Cs<sub>2</sub>CO<sub>3</sub>, acetone, reflux; 88 % (three steps); d) Ag<sub>2</sub>SO<sub>4</sub>/I<sub>2</sub>, MeOH, RT, 1 h; 99 %; e) pinacolotdiborane, [PdCl<sub>2</sub>(dppf)] · CH<sub>2</sub>Cl<sub>2</sub>, KOAc, DMSO, 80 °C, 10 h, 91 %; f) (*E*)-**9**, [PdCl<sub>2</sub>(dppf)] · CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, DME, 80 °C, 2 h; 75 %. Cbz = benzyloxycarbonyl, LDA = lithium diisopropylamide, DMP = 2,2-dimethoxypropane, PPTS = pyridinium *p*-toluenesulfonate, dppf = bis(diphenylphosphanyl)ferrocene.

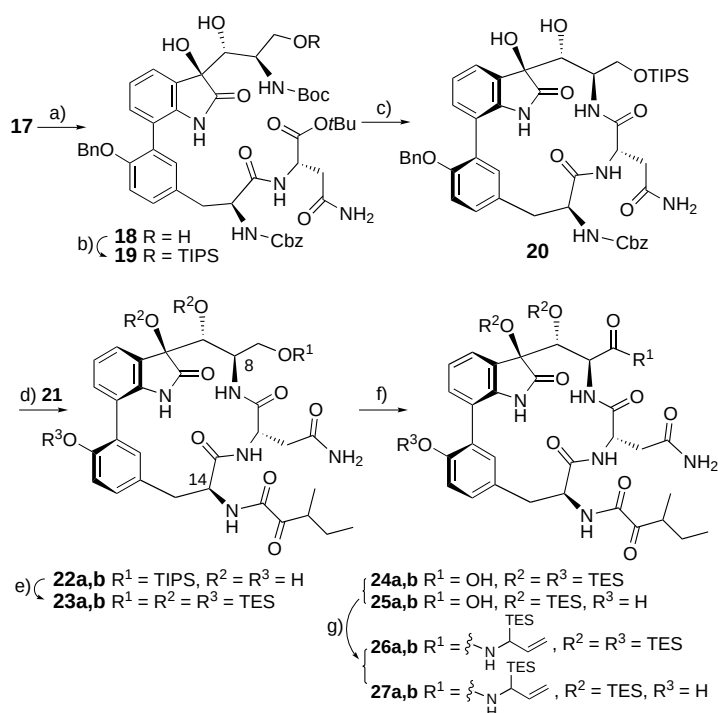
a 1:1.3 mixture of  $\alpha,\beta$ -unsaturated lactams (*Z*)-**9** and (*E*)-**9**.<sup>[4a,e]</sup> Fortunately, the former isomer could be converted to the latter one through iodine-mediated isomerization.<sup>[4a,e]</sup> In a parallel sequence, L-tyrosine (**10**) was converted to **11** in three steps (Scheme 3).<sup>[9]</sup> A high-yielding *ortho* iodination<sup>[4a]</sup> of **11** led to **12** and thence, after palladium-mediated borylation,<sup>[10]</sup> to **13**. Suzuki-type coupling<sup>[11]</sup> of **13** with (*E*)-**9** afforded compound **14** (75 % yield). We hoped that the biaryl domain thus presented would be serviceable in the context of our projected total synthesis (see below).

Hydrolysis of the methyl ester function of **14** led to the corresponding carboxylic acid, which, after acylation of the basic nitrogen atom of the asparagine derivative H-Asn-OrBu (**15**), afforded **16**. The hydroxy groups were introduced at C6 and C7, as shown in Scheme 4. Indeed, the presence of the Garner *N,O*-acetonide served to direct, preferentially, the oxidizing agent to the *Re* face (C6) of **16** to afford **17** in a 5:1 ratio relative to its 6*R*,7*S* stereoisomer (not shown).



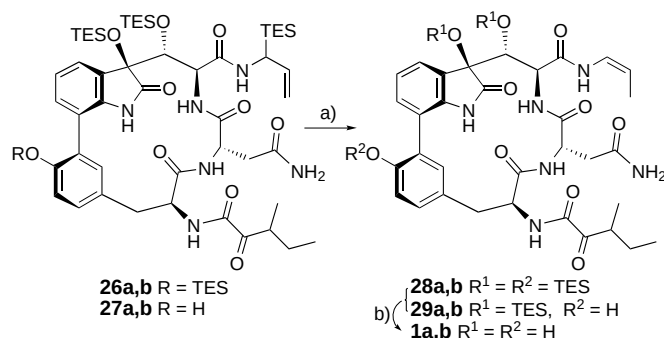
Scheme 4. Synthesis of diol **17**. a) 1) LiOH, THF/H<sub>2</sub>O, 0 °C, 1.5 h; 2) H-Asn-OrBu (**15**), EDC/HOAT, THF, RT, 2 h; 85 % (two steps); b) OsO<sub>4</sub>/NMO, (DHQD)<sub>2</sub>-PHAL, *t*BuOH/H<sub>2</sub>O, RT, 12 h; 88 % (dr = 5:1). Asn = asparagine, NMO = 4-methylmorpholine *N*-oxide, (DHQD)<sub>2</sub>-PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine.

The timing and manner in which the various heteroatom-centered functional groups were exposed and protected proved to be critical to the success of the project. We proceeded as follows (see Scheme 5): Deprotection of the *N,O*-acetonide linkage of **17** afforded *N*-Boc triol **18**. The primary alcohol at position 25 was protected as its TIPS derivative (**19**). Cleavage of the *tert*-butyl group generated a carboxylic acid at C10 which set the stage for macrolactamization (see compound **20**).<sup>[12]</sup> In the next step, the benzyl groups protecting the C19 phenol and N33 were concurrently cleaved by hydrogenolysis. Acylation of the latter basic nitrogen atom with racemic **21**<sup>[13]</sup> afforded **22a** and **22b** as a 1:1 mixture. Both compounds were advanced concurrently. The TIPS protecting group was cleaved from the primary alcohol. The four hydroxy groups (positions 6, 7, 19, and 25) were protected as the TES derivatives (see **23a** and **23b**). In a key step of the synthesis, reaction of these compounds with Jones reagent<sup>[14]</sup> led to specific oxidation at the primary center (position 25) to afford acids **24a** and **24b**. In addition, partial deprotection occurred at the C19 ether linkage which resulted in the formation of **25a** and **25b**. This four-component mixture led, after condensation with amine **6** as indicated, to the amide silyl ethers **26a** and **26b** as well as amide phenols **27a** and **27b** (**26a,b**:**27a,b**  $\approx$  1:1.5).



Scheme 5. Synthesis of  $\alpha$ -silylallyl amides **26a,b** and **27a,b**. a) PPTS/MeOH, reflux, 2 h; b) TIPSCl, imidazole/DMAP, CH<sub>2</sub>Cl<sub>2</sub>, RT, 5 h; 88 % (two steps); c) 1) TFA/CH<sub>2</sub>Cl<sub>2</sub> (4:1), RT, 2 h; 2) EDC/HOAT/DIEA, CH<sub>2</sub>Cl<sub>2</sub>/DMF (2 mM), RT, 24 h; 52 % (two steps); d) 1) Pd/C, H<sub>2</sub>, EtOH, RT, 19 h; 2) (±)-3-methyl-2-oxopentanoic acid (**21**), EDC/HOAT, CH<sub>2</sub>Cl<sub>2</sub>/DMF, RT, 2 h; 85 % (2 steps); e) 1) HF/Py; 2) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → RT, 15 h; 3) NaHCO<sub>3</sub>; 4) citric acid, EtOAc/H<sub>2</sub>O; 73 % (from **22**); f) Jones reagent, acetone, 0 °C, 2 h; g) **6**, EDC/HOAT, CH<sub>2</sub>Cl<sub>2</sub>/DMF, RT, 13 h; 45 % (two steps). DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, DIEA = *N,N*-diisopropylethyl amine.

Construction of the (*Z*)-1-propenylamide was now achieved by thermally driven rearrangement of the  $\alpha$ -silylallyl amides corresponding to **3** (Scheme 6). The rearrangement of



Scheme 6. Synthesis of TMC-95A (**1a**) and TMC-95B (**1b**). a) 1) *o*-xylene, 140 °C, 3 d; 2) H<sub>2</sub>O; b) HF/Py, THF/Py; then Me<sub>3</sub>SiOMe; 49 % (two steps).

the complex mixture<sup>[15]</sup> in anhydrous *o*-xylene at 140 °C provided (*Z*)-1-propenylamides **28a,b** and **29a,b**. The crude mixture of these compounds was globally deprotected with pyridine-buffered HF/pyridine to afford a mixture of our total synthesis goals—TMC-95A and TMC-95B (**1a** and **1b**; 1:1). This mixture was separated by RP-HPLC<sup>[16]</sup> to provide the individual compounds **1a** and **1b**. These were characterized

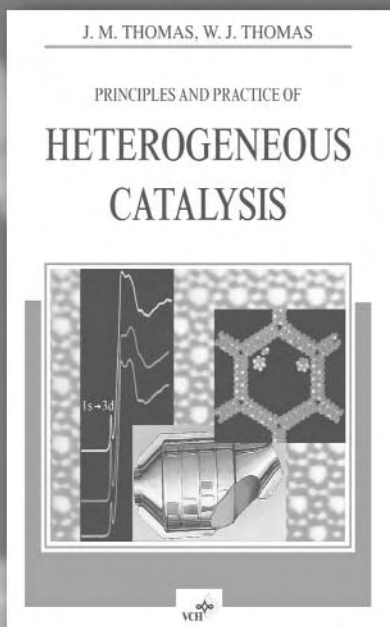
by their high-field NMR spectra in comparison with those of authentic samples.<sup>[16]</sup>

In summary, the total syntheses of TMC-95A and TMC-95B have been achieved. The program featured a sequential assembly of oxindole **7**, Garner's aldehyde (**8**), aryl boronate **13**, asparagine derivative **15**, 3-methyl-2-oxopentanoic acid (**21**), and  $\alpha$ -silylallyl amine **6**. Highlights of the synthesis include a Suzuki biaryl construction ((*E*)-**9** + **13** → **14**), a diastereofacial dihydroxylation reaction that took advantage of the Garner method (**16** → **17**), and a macrolactamization (formation of **20**). We also note that new chemistry to accomplish stereospecific *cis*-propenyl amide formation (**26**/ **27** → **28/29**) was inspired by goal system **1**. The application to the delicate case at hand serves to build confidence in its generality.

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- Amine **6** (S.-F. Chen, E. Ho, P. S. Mariano, *Tetrahedron* **1988**, *44*, 7013–7026) was synthesized by using an improved procedure from allyl alcohol through a one-pot TES ether formation, retro-Brook rearrangement, and mesylation, followed by a displacement of mesylate with ammonia. Acylation in entries 1–4 (Table 1) was accomplished by coupling of **6** with the acid chlorides, while in entry 5 an EDC-mediated coupling with protected amino acid with amine **6** was involved. Details will be forthcoming in a full disclosure.
- The formation of silyl imidates **4** was clearly observed by <sup>1</sup>H NMR spectroscopy when these reactions were carried out in deuterated solvents.
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- The atropisomer shown for **20** follows from the C6 stereochemistry (see ref. [2b]).

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- [15] It was not feasible or necessary to separate at this stage. Rather the eight-component mixture was advanced as shown, and the separation was achieved at the stage of the two-component mixture **1a/1b**.
- [16] HPLC conditions are as follows. Column: YMC-pack ODS-AM, 150 × 10 mm; eluant: 25% MeCN in water; flow rate: 2.5 mL·min<sup>-1</sup>; *t*<sub>R</sub>(**1a**) = 37.3 min, *t*<sub>R</sub>(**1b**) = 34.3 min. The synthetic materials were identical to natural TMC-95A and TMC-95B (TLC, NMR, EIMS, and HPLC). We thank Dr. Jun Kohno, Tanabe Seiyaku Co., Japan, for generously providing us with the HPLC conditions and the samples of TMC-95A and B for comparison.



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