

ANGEWANDTE CHEMIE

A Journal of the
Gesellschaft
Deutscher Chemiker

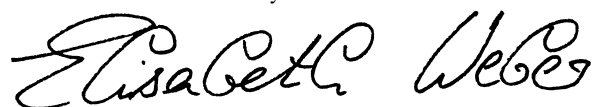
EDITORIAL

Forty years of chemistry—that is the content of this supplement to *Angewandte Chemie International Edition*, which comprises two indexes covering all the review articles of the past forty years sorted according to author names and keywords. As the review articles published in *Angewandte Chemie International Edition* document all the important developments in chemistry and related disciplines you are invited on a discovery tour through the recent history of chemistry. For which of today's hot topics was important preliminary work performed? Which topics have always been in the foreground? Which important subjects emerged recently? Who has published review articles in "Angewandte"? Who has focussed on only one (major) topic throughout his/her career? Who has switched to completely new projects?

What is the reason for presenting forty years of reviews? 1962 was the first year that the English edition of *Angewandte Chemie* was published and in 1992 we published our 30 Year Index of Reviews—at that time sold separately and thus not available everywhere. This time, every subscriber to *Angewandte Chemie International Edition* receives the index of reviews, and naturally it will also be available electronically through Wiley InterScience. In addition, we intend to update the electronic index annually.

The principles behind the indexes are given at the start of each index.

I hope you will enjoy browsing through this index and discover a lot of interesting chemistry and also that this index will be a valuable aid in your search for information.



Elisabeth Weber



Fast ein halbes Jahrhundert Chemiegeschichte halten sie mit diesem Supplement zur *Angewandten Chemie* in Händen, in dem Sie alle Aufsätze der letzten vierzig Jahre nach den Autoren und nach Stichwörtern sortiert finden. Damit können Sie sich auf eine Entdeckungsreise begeben, denn Aufsätze, die in der *Angewandten Chemie* erschienen sind, dokumentieren alle wichtigen Entwicklungen in der Chemie und ihren Nachbardisziplinen. Zu welchen heißen Themen von heute gab es wichtige Vorarbeiten? Welche Themen sind Dauerbrenner? Was waren neue wichtige Forschungsthemen der letzten Jahre? Wer alles hat Aufsätze in der „Angewandten“ publiziert? Welche Forscher haben ihre Interessen über Jahre auf ähnliche Themen konzentriert? Welche wandten sich mehrfach völlig neuen Aufgaben zu?

Doch warum ausgerechnet vierzig Jahre Aufsatzgeschichte? Weil 1962 das erste Jahr war, in dem die *Angewandte Chemie* auch in einer englischen Ausgabe erschien – 1992 Anlass für das 30-Jahre-Aufsatzregister, das allerdings als separates Produkt vermarktet wurde und darum längst nicht überall verfügbar war. Dieses Mal dagegen erhält jeder Abonnent der *Angewandten Chemie* das Aufsatzregister, und natürlich ist es auch elektronisch über Wiley InterScience verfügbar. Außerdem planen wir, es künftig jährlich elektronisch fortzuschreiben.

Die Regeln, die bei der Gestaltung des Registers angewendet wurden, sind vor den beiden Teilregistern kurz erläutert.

Nun wünsche ich Ihnen viele Entdeckungen beim Blättern in diesem Register und viel Nutzen beim gezielten Arbeiten mit ihm.

AUTHOR INDEX

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Each entry in this alphabetically sorted author index gives all authors of a review with the name used for sorting in bold. An asterisk indicates correspondence authors of the review. Next come the title of the review and the year of publication, the volume number, and the page numbers (initial and final), first for the German and then for the international edition. Only the English title is listed for contributions published in both languages. A page number in brackets indicates a corrigendum published in the same volume of the journal.

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- Leitner, W.: **1995**, *107*, 2391–2405; **1995**, *34*, 2207–2221

Carbon disulfide

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Carbonic anhydrase

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Carbon ligands

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Carbonylation

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 α -Carbonyl azo compounds

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Carbonyl compounds

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Carbonyl hydrogenation

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Carbonyl ligands

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Carbonyl methylenation

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Carbonyl olefination

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- Pommer, H.: **1977**, *89*, 437–443; **1977**, *16*, 423–429
- Shemyakin, M. M.: **1964**, *76*, 113–123; **1964**, *3*, 250–260

Carbonyl oxides

- Sander, W.: **1990**, *102*, 362–372; **1990**, *29*, 344–354

N-Carbonylsulfamoyl chloride

- Graf, R.: **1968**, *80*, 179–189; **1968**, *7*, 172–182

Carbonyl ylides

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Carboranes

- Köster, R.: **1967**, *79*, 197–219; **1967**, *6*, 218–240

Carbosilanes

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Carboxylic acids

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- Möller, K. E.: **1963**, *75*, 1098–1101; **1963**, *2*, 719–722
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Carbyne ligands

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Casein

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Catalysis

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- Brown, M. S.: **1986**, *98*, 579–599; **1986**, *25*, 583–602
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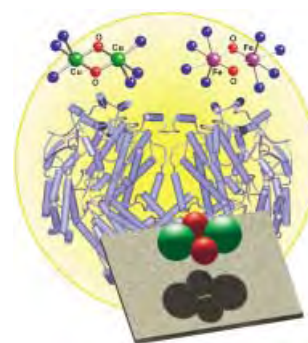
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COVER PICTURE

The cover picture shows $\text{Cu}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})_2$ complexes with the $\text{M}_2(\mu\text{-O})_2$ diamond core motif (the core is shown bottom right, M = green and oxygen = red spheres) and a representative example of a non-heme multimetal enzyme (hydroxylase component of methane monooxygenase, in the background). Although quite a familiar feature in high-valent manganese chemistry, the $\text{M}_2(\mu\text{-O})_2$ diamond core motif has only recently been found in synthetic complexes for M = Cu or Fe. Despite differences in electronic structures that have been revealed through experimental and theoretical studies, $\text{Cu}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})_2$ cores exhibit analogously covalent metal-oxo bonding, and similar tendencies to abstract hydrogen atoms from substrates. Our understanding of biocatalysis has been enhanced significantly through the isolation and comprehensive characterization of the $\text{Cu}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})_2$ complexes. In particular, it has led to the development of new mechanistic notions about how non-heme multimetal enzymes, such as, methane monooxygenase, fatty acid desaturase, and tyrosinase, may function in the activation of dioxygen to catalyze a diverse array of organic transformations. To find out more see the review by L. Que, Jr. and W. B. Tolman on p.1114 ff.



REVIEWS

Contents

A complex and sophisticated machinery of proteins is involved in cellular protein folding and allows the functional state of proteins to be maintained under conditions in which they would normally unfold and aggregate. The structure of such a system, the small heat-shock protein from the archaeon *Methanococcus jannaschii*, is depicted. The principle features of these molecular chaperones, their structure–activity relationships, and the underlying molecular mechanisms are discussed in this review.



Angew. Chem. 2002, 114, 1142–1158

S. Walter, J. Buchner* 1098–1113

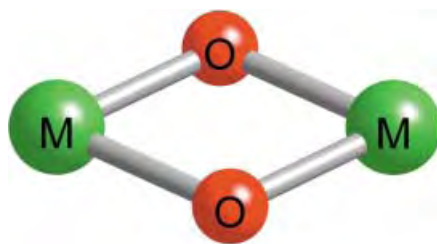
Molecular Chaperones—Cellular
Machines for Protein Folding

Keywords: chaperone proteins • protein
aggregation • protein folding • protein
structures • structure–activity
relationships

Diamonds with iron and copper:

The recent characterization of meta-stable iron and copper complexes with the diamond-shaped bis(μ -oxo) core (see picture) has provided new insights into dioxygen activation and catalysis at dimetal sites in proteins. Recent detailed studies have shown that the iron and copper compounds have divergent electronic structures, yet exhibit a number of related structural features, spectroscopic properties, and modes of reactivity.

Angew. Chem. **2002**, *114*, 1160–1185



L. Que, Jr.,* W. B. Tolman* . 1114–1137

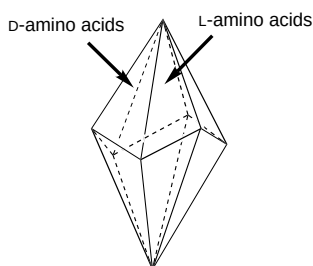
Bis(μ -oxo)dimetal “Diamond” Cores in Copper and Iron Complexes Relevant to Biocatalysis

Keywords: bioinorganic catalysis • copper • iron • metalloenzymes • metal–oxo complexes • oxygen activation

MINIREVIEW

Chirality existed before hands developed: Molecular chirality constitutes a fascinating topic linked to the origin of life itself. This minireview highlights some of the recent developments in this area which in part rediscover past reflections and achievements, and approaches the question whether the chirality of living systems arises from subtle quantum–electroweak force effects or from a more familiar chemistry, specifically the chiroselective adsorption of some amino acids onto minerals with enantiomeric faces (see picture).

Angew. Chem. **2002**, *114*, 1187–1193



P. Cintas* 1139–1145

Chirality of Living Systems: A Helping Hand from Crystals and Oligopeptides

Keywords: autocatalysis • biomineralization • chirality • origin of life • prebiotic chemistry

VIPs

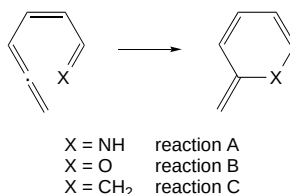
The following communications are “Very Important Papers” in the opinion of two referees. They will be published shortly (those marked with a diamond will be published in the next issue). Short summaries of these articles can be found on the *Angewandte Chemie* homepage at the address <http://www.angewandte.com>

Semiconductor Nanohelices Templated by Supramolecular Ribbons	E. D. Sone, E. R. Zubarev, S. I. Stupp*	◆
Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems	V. V. Borovkov,* T. Harada, Y. Inoue, R. Kuroda*	◆
The Stable Pentamethylcyclopentadienyl Cation	J. B. Lambert,* L. Lin, V. Rassolov	
Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer	S. Liu, S. P. Armes*	◆
Cyclo[8]pyrrole: A Simple-to-Make Expanded Porphyrin with No Meso Bridges	D. Seidel, V. Lynch, J. L. Sessler*	◆
Cyclotetrasilene Ion: A Reversible Redox System of Cyclotetrasilene Cation, Radical, and Anion	T. Matsuno, M. Ichinohe, A. Sekiguchi*	
Synthesis and Structure of Na ₃ N	D. Fischer, M. Jansen*	

CORRESPONDENCE



A reanalysis of the results obtained by Cossío and de Lera et al. show that reactions A and B (see scheme) are essentially pericyclic even though they are favored by the electron lone pair on the heteroatom. This lone pair provides a reaction path with a decreased energy investment but the essential features of the process are typical of a disrotatory electrocyclicization as in reaction C.



Angew. Chem. **2002**, *114*, 1195–1198

Different assumptions and considerations used in the calculations of Rodríguez-Otero and Cabaleiro-Lago account for the different interpretations of the mechanism for reactions A and B (see scheme). However, the authors believe that geometric, electronic, orbital, and magnetic criteria indicate that reactions A and B take place by a pseudopericyclic mechanism, whereas the all-carbon equivalent (reaction C) corresponds to a disrotatory (aromatic) electrocyclicization.

Angew. Chem. **2002**, *114*, 1198–1200

J. Rodríguez-Otero,*
E. M. Cabaleiro-Lago 1147–1150

Electrocyclization of (Z)-1,2,4,6-Heptatetraene and its Heterosubstituted Analogues: Pericyclic or Pseudopericyclic?

A. R. de Lera, F. P. Cossío* . 1150–1152

Reply

Keywords: ab initio calculations • aromaticity • density functional calculations • electrocyclic reactions • transition states

COMMUNICATIONS

Immobilized gold nanoparticles on a three-dimensionally ordered macroporous (3DOM) film were prepared by a dipping method. The localized surface plasmon resonance of the nanoparticles and the stop-band of the 3DOM film, both still evident after immobilization, are both dependent on the refractive index of the surrounding medium. The picture shows a 3DOM film before (left) and after (right) coating with gold nanoparticles.



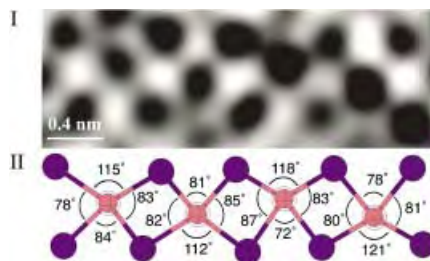
Angew. Chem. **2002**, *114*, 1201–1204

Z.-Z. Gu, R. Horie, S. Kubo, Y. Yamada, A. Fujishima, O. Sato* 1153–1156

Fabrication of a Metal-Coated Three-Dimensionally Ordered Macroporous Film and its Application as a Refractive Index Sensor

Keywords: colloids • gold • nanostructures • sensors • UV/Vis spectroscopy

Unknown in bulk BaI₂: Ba coordination numbers of 5 and 6 are present in the one-dimensional (1D) crystal chains formed by BaI₂ within single-walled carbon nanotubes (SWNTs). This is revealed by high-resolution transmission electron microscopy images (I). The derived structure model II shows the bond angles measured for equatorial BaI₄ units along the central 1D octahedral chain within the BaI₂ chain in an SWNT capillary.



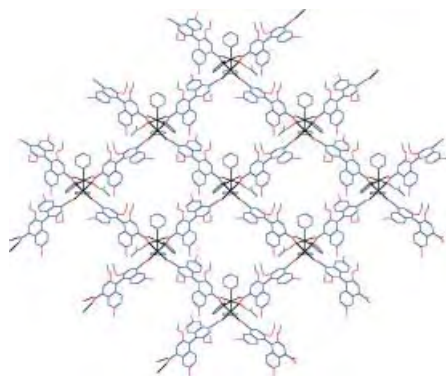
J. Sloan,* S. J. Grosvenor, S. Friedrichs, A. I. Kirkland, J. L. Hutchison, M. L. H. Green 1156–1159

A One-Dimensional BaI₂ Chain with Five- and Six-Coordination, Formed within a Single-Walled Carbon Nanotube

Keywords: barium • electron microscopy • halides • nanotubes



A chiral two-dimensional network is the basis for the structure of a homochiral solid exploiting metal–carboxylate coordination. The synthesis involved enantiopure bridging ligands and metal–organic secondary building units (SBUs), and resulted in ethoxy-protected BINOL functionalities pointing into the cavities in this crystalline chiral zeolitic material (see picture).



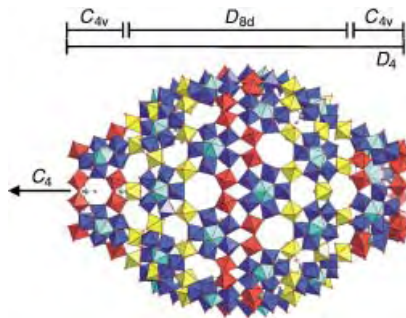
Angew. Chem. **2002**, *114*, 1207–1210

Y. Cui, O. R. Evans, H. L. Ngo,
P. S. White, W. Lin * 1159–1162

Rational Design of Homochiral Solids
Based on Two-Dimensional Metal
Carboxylates

Keywords: chirality • coordination
polymers • crystal engineering •
supramolecular chemistry • zeolite
analogues

Molybdenum monsters: A huge molybdenum cluster, comprising large areas with different local symmetry (in the picture different colors represent different (smaller) Mo fragments) is prepared and characterized. Molybdate fragments, which can tolerate a change of electron density at various positions, can be linked in a tremendous variety of ways according to a split-and-link process. Small changes of the boundary conditions, especially the redox conditions, which control growth, as well as the H^+ ion concentration, can have a deciding influence on the process.



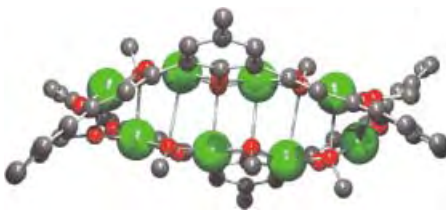
Angew. Chem. **2002**, *114*, 1210–1215

A. Müller,* E. Beckmann, H. Bögge,
M. Schmidtman, A. Dress . 1162–1167

Inorganic Chemistry Goes Protein Size:
A Mo_{368} Nano-Hedgehog Initiating
Nanotechnology by Symmetry Breaking

Keywords: nanostructures •
polyoxometalates • self-assembly •
symmetry breaking • topology

A space-ship-like Cu_8 cluster (see picture) results from the linking of two linear $[Cu_4^I]$ units previously assembled through the template action of a pentadentate O ligand. The core of the cluster represents an entirely new topology within the vast family of magnetically coupled Cu aggregates. The alkoxide-bridged octanuclear units are connected to each other by nitrate ligands into an unprecedented cluster polymer.



Angew. Chem. **2002**, *114*, 1216–1218

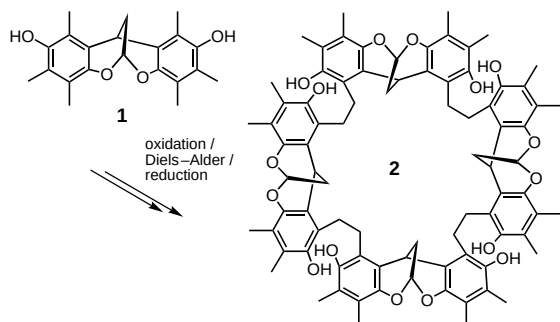
G. Aromí, P. Gamez, O. Roubeau,
H. Kooijman, A. L. Spek, W. L. Driessen,
J. Reedijk * 1168–1170

Ligand-Templated Four-Metal Chains
Dimerize into a Unique $[Cu^I_8]$ Cluster

Keywords: cluster compounds • copper •
magnetochemistry • supramolecular
chemistry • template effect



It might not be as healthy as vitamin E, but the α -tocopherol derivative **1** undergoes all the typical reactions of the vitamin twice, as a result of its “siamese twin” character. The transformation of **1** in a three-step reaction sequence of oxidation, hetero-Diels–Alder reaction, and reduction provides facile access to tetrameric calixarene-type macrocycles **2**.



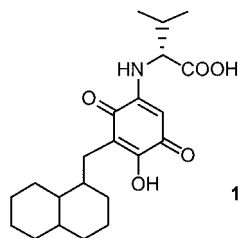
Angew. Chem. **2002**, *114*, 1219–1221

T. Rosenau, A. Potthast, A. Hofinger,
P. Kosma * 1171–1173

Calixarene-Type Macrocycles by
Oxidation of Phenols Related to
Vitamin E

Keywords: cycloaddition • Diels–Alder
reaction • macrocycles • spiro
compounds • vitamin E

Blood and lymph vessel growth is regulated by Tie-2 and the VEGFR-3 receptor tyrosine kinases. These proteins also play major roles in the growth and metastasis of cancers. A novel class of inhibitors of these signal-transducing proteins, and of the IGF1R kinase (such as **1**), is identified from a natural product derived compound library. This discovery opens up new opportunities for the development of antitumor agents.



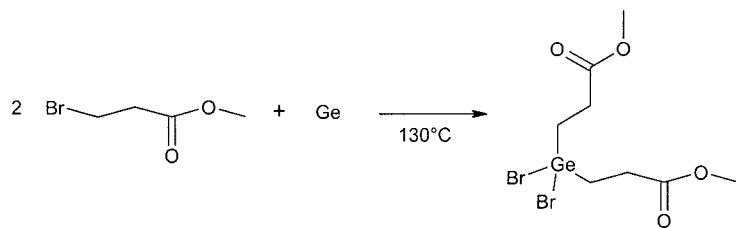
P. Stahl, L. Kissau, R. Mazitschek, A. Gianni,* H. Waldmann* 1174–1178

Natural Product Derived Receptor Tyrosine Kinase Inhibitors: Identification of IGF1R, Tie-2, and VEGFR-3 Inhibitors

Keywords: angiogenesis • antitumor agents • combinatorial chemistry • natural products • tyrosine kinases

Angew. Chem. **2002**, *114*, 1222–1226

Kinetic inertness overcome: The selective coupling of Ge–E bonds (E = halogen, C) can be achieved at 130°C by direct synthesis from activated germanium. Alkyl bromides with an additional carbonyl function (see scheme) can be converted in a controlled manner into dibromodiorganogermanes.



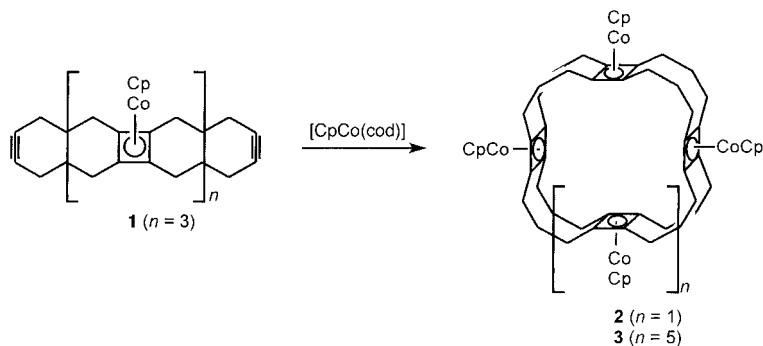
Angew. Chem. **2002**, *114*, 1237–1239

S. Schlecht* 1178–1180

Selective Direct Synthesis of Organofunctionalized Dialkylgermanes from Solvochemically Activated Germanium

Keywords: amorphous materials • direct synthesis • germanium • main group elements

Adjustable belts: Selective synthesis of beltlike cyclophanes containing organo-metallic π systems is now possible. Intra- and intermolecular ring closure of the flexible ten-membered ring units of **1** leads to tetramer **2** and octamer **3**, respectively (see picture; cod = cyclooctadiene).



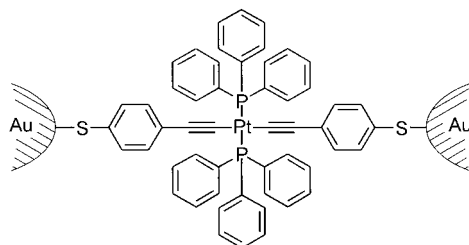
Angew. Chem. **2002**, *114*, 1231–1234

R. J. Schaller, R. Gleiter,* J. Hofmann, F. Rominger 1181–1183

Beltlike Macrocycles with Four and Eight (Cyclopentadienyl)(cyclobutadienyl)-cobalt Building Blocks, Formed by Stepwise Oligomerization of 1,6-Cyclodecadiyne Units

Keywords: alkynes • cobalt • cycloaddition • cyclophanes • macrocycles

A further component for molecular electronics: A single molecule insulator is realized by immobilizing a platinum(II) complex between two gold electrodes (see picture). The current/voltage characteristics of the setup shows the typical behavior of an insulator with a tunnel barrier height of 2.5 eV.



M. Mayor,* C. von Hänisch, H. B. Weber,* J. Reichert, D. Beckmann 1183–1186

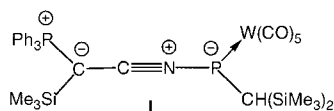
A *trans*-Platinum(II) Complex as a Single-Molecule Insulator

Keywords: electron transport • insulators • molecular electronics • platinum • single-molecule studies

Angew. Chem. **2002**, *114*, 1228–1231

Terminal addition of an electrophilic phosphanediyl complex to the nitrile-nitrogen atom of a Wittig ylide yields the nitrilium phosphane ylide complex **I** as an intermediate. Intramolecularly trapping of **I** by a [3+2] cycloaddition with a *P*-phenyl group leads to a bowl-shaped, coordinatively bonded, novel tricycle.

Angew. Chem. **2002**, *114*, 1226–1228



N. Hoffmann, P. G. Jones,
R. Streubel* 1186–1188

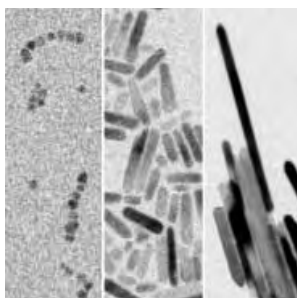
Intramolecular [3+2] Cycloaddition of a Nitrilium Phosphane Ylide Complex to the *P*-Phenyl Group of a Wittig Ylide

Keywords: cycloaddition • 1,3-dipoles • nitrogen heterocycles • phosphorus heterocycles • ylides



Oriented attachment is the key: Single crystalline ZnO nanorods with lengths up to 500 nm could be prepared in a stepwise manner from quasi-spherical nanoparticles. Only after the formation of pearl-chain-like structures (left), do the aggregated particles fuse upon heating to form nanorods (center and right).

Angew. Chem. **2002**, *114*, 1234–1237



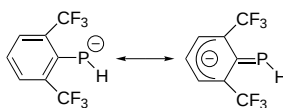
C. Pacholski, A. Kornowski,
H. Weller* 1188–1191

Self-Assembly of ZnO: From Nanodots to Nanorods

Keywords: colloids • crystal growth • nanostructures • oxides • zinc

The electronic and steric properties of the 2,6-bis(trifluoromethyl)phenyl (Ar_t) substituent stabilize a naked dicoordinate phosphorus anion (see scheme) in the primary phosphanide salt $[\text{K}([15]\text{crown-5})_2][\text{Ar}_t\text{PH}]$, both in the solid state and in solution.

Angew. Chem. **2002**, *114*, 1241–1243

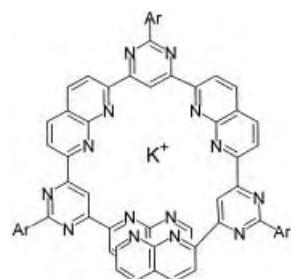


V. L. Rudzevich, H. Gornitzka,
K. Miqueu, J.-M. Sotiropoulos,
G. Pfister-Guillouzo, V. D. Romanenko,
G. Bertrand* 1193–1195

The First “Naked” Primary Phosphanide Anion $[\text{ArPH}]^-$

Keywords: acidity • anions • coordination modes • phosphanides • phosphorus

Alternating naphthyridine–pyrimidine strands self-organize into a helical conformation containing a strongly polar cavity. The binding of metal and ammonium cations promotes supramolecular self-assembly in a sort of effector-induced growth process to form polymolecular stacks (see schematic representation) and fibers observable by electron microscopy. Such entities offer features of molecular ion channels.



Angew. Chem. **2002**, *114*, 1243–1246

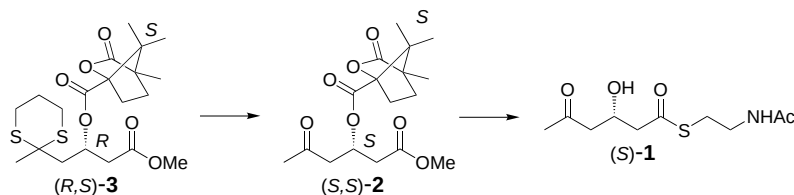


A. Petitjean, L. A. Cuccia,
J.-M. Lehn,* H. Nierengarten,
M. Schmutz 1195–1198

Cation-Promoted Hierarchical Formation of Supramolecular Assemblies of Self-Organized Helical Molecular Components

Keywords: cations • helical structures • heterocycles • self-assembly • supramolecular chemistry

Chirality resolved: The stereochemistry of potential intermediates in the enzymic synthesis of 6-methyl salicylic acid, (*R*)-**1** and (*S*)-**1**, has been determined by X-ray crystallography of two corresponding crystalline intermediates (*S,S*)-**2** (shown) and (*S,S*)-**3** (not shown).



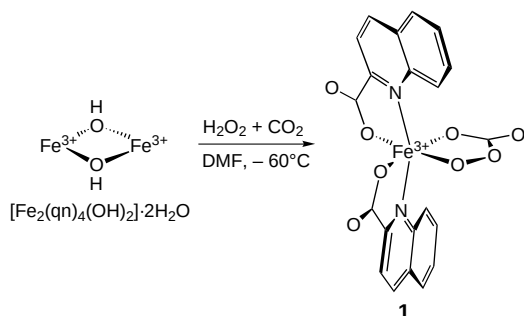
Angew. Chem. **2002**, *114*, 1246–1250

K.-M. Cheung, S. J. Coles,
M. B. Hursthouse, N. I. Johnson,
P. M. Shoolingin-Jordan* ... 1198–1202

The Determination of the Absolute Configurations of Diastereomers of (*S*)-Camphanoyl 3-Hydroxy-5-oxohexanoic Acid Derivatives by X-ray Crystallography

Keywords: chiral auxiliaries • configuration determination • enzymes • polyketides • X-ray diffraction

Stabilization of a peroxocarbonate ligand by formation of a five-membered chelate ring. The mononuclear peroxocarbonate complex **1** was prepared by the reaction of a bis(μ -hydroxo)diiron(III) complex with H_2O_2 and CO_2 . Compound **1** is the first crystallographically characterized transition metal complex with a peroxocarbonate ligand. Formation of the peroxocarbonate moiety in **1** proceeds by a nucleophilic addition of a peroxide anion to CO_2 . Hqn = quinaldic acid.



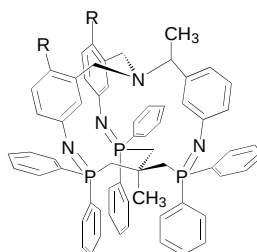
Angew. Chem. **2002**, *114*, 1250–1253

K. Hashimoto, S. Nagatomo, S. Fujinami,
H. Furutachi, S. Ogo, M. Suzuki,*
A. Uehara, Y. Maeda, Y. Watanabe,*
T. Kitagawa* 1202–1205

A New Mononuclear Iron(III) Complex Containing a Peroxocarbonate Ligand

Keywords: iron • oxygen activation • peroxo ligands • Raman spectroscopy • X-ray diffraction

Highly efficient chirality transfer is employed in controlling the topological asymmetry of chiral cages with propeller-like shape and pseudo C_3 symmetry (see picture; $R = \text{H, Cl}$). The cages are formed when two tripodal units (a tribenzylamine and a tris(tertiary phosphane)) become linked by three $\text{P}=\text{N}$ bonds, by means of a tripod–tripod coupling process followed by a remarkable triple expulsion of molecular nitrogen.



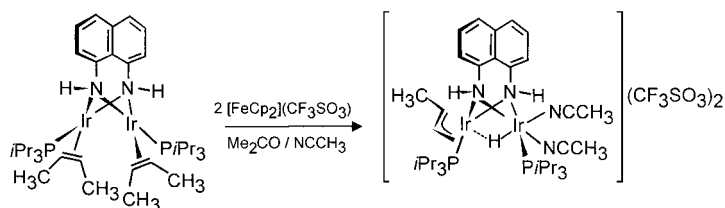
Angew. Chem. **2002**, *114*, 1253–1256

M. Alajarín,* C. López-Leonardo,
A. Vidal, J. Berná,
J. W. Steed* 1205–1208

Helical Sense Bias Induced by Point Chirality in Cage Compounds

Keywords: cage compounds • chirality • cooperative effects • helical structures • phosphazenes

Oxidation favors oxidative addition: This unexpected behavior has been observed in d^8d^8 ‘open-book’ diiridium complexes with alkene ligands, which become C–H activating after oxidation with ferrocenium salts (see scheme).



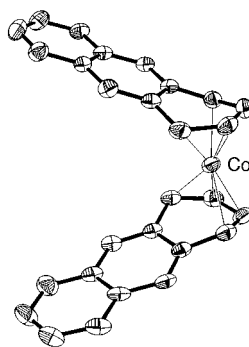
Angew. Chem. **2002**, *114*, 1256–1259

M. V. Jiménez, E. Sola, J. Caballero,
F. J. Lahoz, L. A. Oro* 1208–1211

Alkene C–H Activations at Dinuclear Complexes Promoted by Oxidation

Keywords: C–H activation • hydride ligands • iridium • metal–metal interactions • oxidation

Two remarkable features of bis(anthracene)-cobaltate(1[−]) (see picture) are that it is the first homoleptic anthracene transition metal complex to be prepared by a conventional synthesis, that is, one not involving a metal atom reactor, and it is the first anionic complex of a late (Groups 7–11) transition metal containing only bound aromatic hydrocarbons.



W. W. Brennessel, V. G. Young, Jr.,
J. E. Ellis* 1211–1215

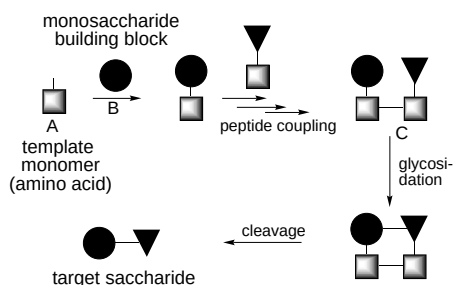
Bis(1,2,3,4- η^4 -anthracene)cobaltate(1[−])

Keywords: arene ligands • cobalt • diene ligands • isocyanide ligands • phosphane ligands

Angew. Chem. **2002**, *114*, 1259–1263



“Zipping up” a carbohydrate can be as simple as glycosidation of sugar units that are attached to a solid-phase bound peptide framework (see schematic presentation). The target disaccharides can be prepared efficiently, and the peptide template was found to influence the stereoselectivity of the glycosidation process.



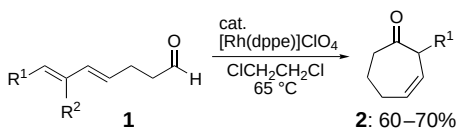
D. R. Greenwell, A. F. Ibnouzak, S. L. Warriner* 1215–1218

Peptide-Templated Saccharide Synthesis on a Solid Support

Keywords: carbohydrates • peptides • solid-phase synthesis • synthetic methods • template synthesis

Angew. Chem. **2002**, *114*, 1263–1266

The size of the ring formed in the Rh^I-catalyzed intramolecular hydroacylation of 4,6-dienals is dependent on the presence of a substituent at C7 and the geometry of the olefin. Cyclization of 4,6-dienals with a substituent at the C7 position (**1**; R¹ = alkyl, R² = H) produced cycloheptenones (**2**) as the major product (see scheme), while that of 4,6-dienals with no substituent at the terminus of the diene (**1**; R¹ = H) preferentially gave cyclopentanones. The cyclization of substrates containing a 6*E* olefin produced cycloheptenones as the major product, while a cyclopentanone was obtained from a substrate having a 6*Z* olefin. dppe = 1,2-bis(diphenylphosphanyl)ethane.



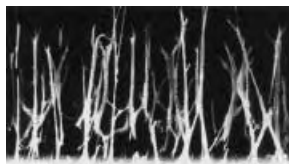
Y. Sato, Y. Oonishi, M. Mori* 1218–1221

A New Method for the Synthesis of Cycloheptenones by Rh^I-Catalyzed Intramolecular Hydroacylation of 4,6-Dienals

Keywords: aldehydes • cyclization • dienes • hydroacylation • rhodium

Angew. Chem. **2002**, *114*, 1266–1269

A water contact angle exceeding 170° is exhibited by the surface of aligned polyacrylonitrile (PAN) nanofibers without any surface treatment (the picture shows a cross-sectional view of the as-synthesized nanofibers). The nanofibers were obtained by simply extruding a PAN solution through an anodic alumina template into a solidifying solution. The factors that govern the hydrophobicity of aligned nanostructures are discussed.



L. Feng, S. Li, H. Li, J. Zhai, Y. Song, L. Jiang,* D. Zhu 1221–1223

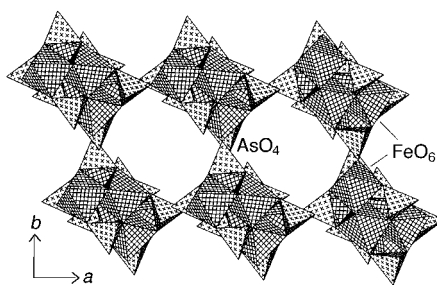
Super-Hydrophobic Surface of Aligned Polyacrylonitrile Nanofibers

Keywords: electron microscopy • hydrophobic effect • nanostructures • surface chemistry

Angew. Chem. **2002**, *114*, 1269–1271

Three-dimensions from one: One-dimensional iron arsenate oxalate is prepared, and shown to be reactive, giving rise to a two- and a mixed-valent ($\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$) three-dimensional iron arsenate structure (see picture). The sequential crystallization provides evidence for the building up of open architectures from low to higher dimensional structures, demonstrating the “life of a chemical system”.

Angew. Chem. **2002**, *114*, 1272–1274



S. Chakrabarti,
S. Natarajan* 1224–1226

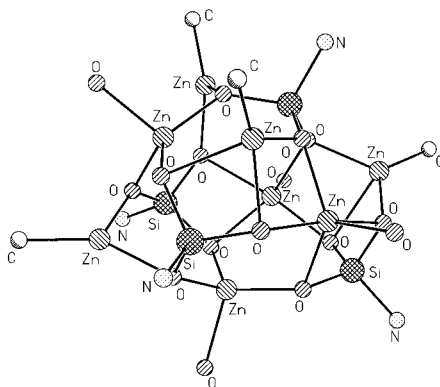
A Reactive Intermediate in the Synthesis of Iron Arsenates: Synthesis of the First One-Dimensional Iron Arsenate Oxalate and Its Transformation into Two- and Three-Dimensional Iron Arsenates

Keywords: crystal growth • iron • microporous materials • mixed-valent compounds • solid-state structures



Zinc atoms in three different geometries and chemically diverse coordination environments are present in the title compound (see structure). This octanuclear zinc siloxane compound was prepared by the addition of excess Me_2Zn to $\text{RSi}(\text{OH})_3$ ($\text{R} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3\text{N}(\text{SiMe}_3)$) (2:1) in THF:hexane at room temperature. This method provides a route to larger aggregates of such compounds.

Angew. Chem. **2002**, *114*, 1274–1277



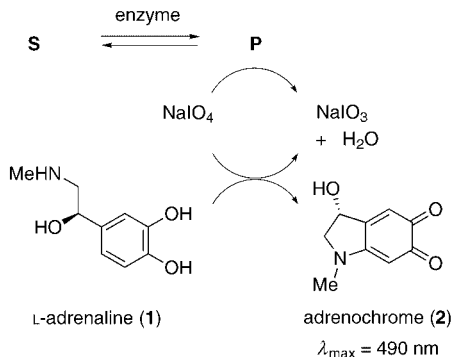
G. Anantharaman, H. W. Roesky,*
J. Magull 1226–1229

$[\text{Zn}_4(\text{thf})_4(\text{MeZn})_4(\text{O}_3\text{SiR})_4]$ ($\text{R} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3\text{N}(\text{SiMe}_3)$), A Compound Containing Trigonal-Planar, Tetrahedral, and Trigonal-Bipyramidal Metal Atoms: A New Route to Larger Aggregates

Keywords: aggregation • cage compounds • silicon • zinc

A versatile high-throughput enzyme assay is demonstrated which is based on the colorimetric back-titration of sodium periodate with L-adrenaline (**1**). Enzyme activity is associated with the depletion of sodium periodate by the reaction product (**P**), and indicated by the decrease in the amount of the red dye adrenochrome (**2**) produced by the oxidation of adrenaline by sodium periodate.

Angew. Chem. **2002**, *114*, 1277–1280



D. Wahler, J.-L. Reymond* . 1229–1232

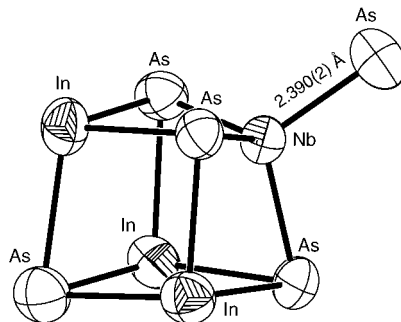
The Adrenaline Test for Enzymes

Keywords: enzyme assays • high-throughput screening • hydrolases • lipases • phytases



The “uneven” cubane of three indium, four arsenic, and one niobium atom has a handle of a fifth arsenic atom multiply bonded to the niobium corner (see structure).

Angew. Chem. **2002**, *114*, 1280–1282



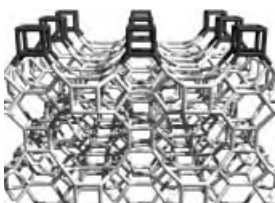
F. Gascoin, S. C. Sevov* 1232–1234

Cubane with a Handle:
 $[\{\text{In}_3\text{As}_4\text{Nb}\}-\text{As}]^{7-}$ in $\text{Cs}_7\text{NbIn}_3\text{As}_5$

Keywords: arsenic • multiple bonds • polyanions • solid-state structures • Zintl phases



New insights into crystal growth for zeolite Beta C are shown from simulation studies. Crystal growth may be facilitated by double 4-rings (see picture), giving rise to two distinct external surface topologies. The predictions concur with and explain recent experimental findings and provide evidence that the nanoscopic surface structures arise from complex reactions of siliceous oligomers with the zeolite surface.



B. Slater,* C. R. A. Catlow, Z. Liu,
T. Ohsuna, O. Terasaki,
M. A. Camblor 1235–1237

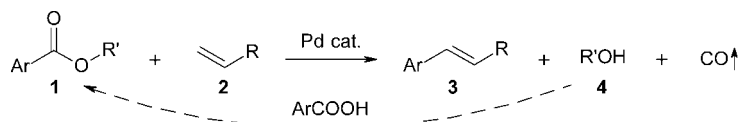
Surface Structure and Crystal Growth of
Zeolite Beta C

Keywords: computer chemistry • crystal growth • surface chemistry • zeolites

Angew. Chem. **2002**, *114*, 1283–1285



Easy and clean: A palladium(0)-catalyzed decarbonylative Heck olefination of activated esters of aryl, heteroaryl, and vinyl carboxylic acids opens up an opportunity for a novel waste-free Heck olefination process (see scheme).



L. J. Goossen,* J. Paetzold .. 1237–1241

Pd-Catalyzed Decarbonylative
Olefination of Aryl Esters: Towards a
Waste-Free Heck Reaction

Keywords: arenes • esters • Heck reaction • homogeneous catalysis • palladium

Angew. Chem. **2002**, *114*, 1285–1289



Stabilization of electron-hole pairs for more than 12 months at room temperature was achieved by using biphenyl molecules occluded in the Al-ZSM-5 zeolite type (see picture). The unpaired electrons are localized in the zeolite framework in the vicinity of the occluded biphenyl molecule. Results establish that the trapped electron-hole pair acquires a ferromagnetic ground state.



A. Moissette,* H. Vezin, I. Gener,
J. Patarin, C. Brémard 1241–1244

Electron-Hole Pairs Stabilized in Al-
ZSM-5 Zeolites

Keywords: biphenyl • electron transfer • EPR spectroscopy • Raman spectroscopy • zeolites

Angew. Chem. **2002**, *114*, 1289–1292



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(see article for access details).

* Author to whom correspondence should be addressed



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<http://vigen.biochem.vt.edu/xpd/xpd.htm>

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H. Waldmann, L. Kissau 1251

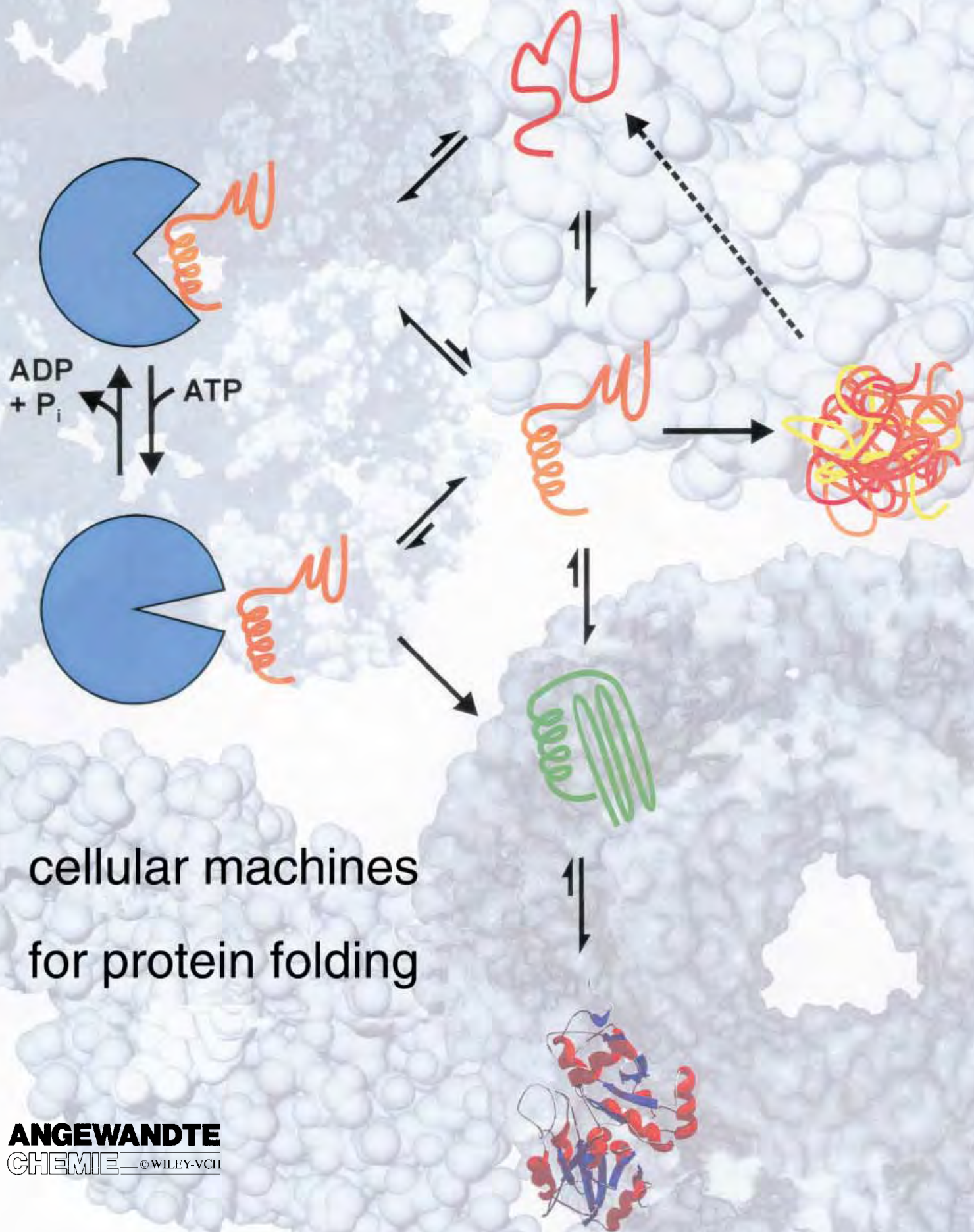
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Issue 5, 2002 was published online on March 7.
Issue 6, 2002 was published online on March 15.

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Molecular Chaperones



Molecular Chaperones—Cellular Machines for Protein Folding

Stefan Walter and Johannes Buchner*

Proteins are linear polymers synthesized by ribosomes from activated amino acids. The product of this biosynthetic process is a polypeptide chain, which has to adopt the unique three-dimensional structure required for its function in the cell. In 1972, Christian Anfinsen was awarded the Nobel Prize for Chemistry for showing that this folding process is autonomous in that it does not require any additional factors or input of energy. Based on *in vitro* experiments with purified proteins, it was suggested that the correct three-dimensional structure

can form spontaneously *in vivo* once the newly synthesized protein leaves the ribosome. Furthermore, proteins were assumed to maintain their native conformation until they were degraded by specific enzymes. In the last decade this view of cellular protein folding has changed considerably. It has become clear that a complicated and sophisticated machinery of proteins exists which assists protein folding and allows the functional state of proteins to be maintained under conditions in which they would normally unfold and aggregate. These proteins are collectively

called molecular chaperones, because, like their human counterparts, they prevent unwanted interactions between their immature clients. In this review, we discuss the principal features of this peculiar class of proteins, their structure–function relationships, and the underlying molecular mechanisms.

Keywords: chaperone proteins • protein aggregation • protein folding • protein structures • structure–activity relationships

1. Protein Folding and Molecular Chaperones

Whereas many proteins can be refolded *in vitro* under optimized conditions in good yields, the situation in a living cell is less favorable. In particular, high protein concentration and temperature promote aggregation as an undesired side reaction, competing with productive folding.^[1, 2] Unlike protein assembly, which describes the ordered association of several polypeptide chains into a defined functional oligomer, aggregation is the disordered, non-specific association of polypeptide chains which leads to the formation of heterogeneous protein particles devoid of any biological function.

Considering the amount of energy the cell has already invested in the synthesis of a new polypeptide, it does not come as a surprise that strategies have evolved to promote the productive folding of a protein into its active conformation. During molecular evolution, polypeptide sequences were likely not only selected based on their biological properties, but also on whether they can fold productively. To increase the accessible conformation space, cells developed molecular

chaperones, a set of proteins that associate with unfolded polypeptides thereby preventing aggregation and promoting productive folding in an ATP-dependent manner.^[3, 4]

1.1. Protein Folding In Vitro

Information transfer from DNA to mRNA and from mRNA to the polypeptide employs molecular complementarity and the genetic code. It translates the linear sequence of base triplets into a linear sequence of amino acids. The final step in the process from gene to the functional protein, protein folding, converts this linear information into a three-dimensional structure. This reaction turned out to be very complex. Although we have learned much over the past decades about the physical principles underlying the folding process,^[5–8] it is still a major challenge for biochemists to predict the structure into which a given polypeptide will fold.

The investigation of the protein-folding problem began in the 1960s with the groundbreaking experiments of Christian Anfinsen and co-workers on the reversible folding of an abundant RNA-cleaving enzyme, ribonuclease A (RNase A).^[9, 10] Incubation with urea (8M) and a reducing agent resulted in an unfolded protein without any disulfide bonds or enzymatic activity. This denatured state of RNase A is thought to resemble the conformation immediately after its

[*] Prof. Dr. J. Buchner, Dr. S. Walter
Institut für Organische Chemie & Biochemie
Technische Universität München
Lichtenbergstr. 4, 85747 Garching (Deutschland)
Fax: (+49) 89-289-13345
E-mail: johannes.buchner@ch.tum.de

synthesis on the ribosome. When the denaturant and the reducing agent were removed by dialysis in Anfinsen's experiment, the enzyme was found to slowly regain its activity. Apparently, it had refolded *in vitro*. This observation clearly showed that the three-dimensional structure of this protein is encoded in its amino acid sequence, and that no other factors are required for structure acquisition. Thus, protein folding is an autonomous and, given the proper conditions, spontaneous process. Following the work of Anfinsen and co-workers, biochemists studying the folding properties of other small, monomeric proteins were able to confirm his observations.^[11, 12] Eventually, these results led to the notion that, in principle, every protein can be refolded *in vitro*.^[13, 14]

The native state of a protein corresponds to a fairly narrow energy minimum on the conformational energy landscape.^[5, 15] The denatured state, on the other hand, is represented by a large ensemble of conformations with high internal energy and flexibility. During the folding process, numerous noncovalent interactions are formed that require the exact positioning of the various atoms of the protein. Among these, the hydrophobic interactions seem to play an important role.^[16] Hydrophobic molecules tend to associate with each other in a polar environment for reasons of entropy and enthalpy. Accordingly, hydrophobic amino acids are predominantly found in the core of a folded protein. When biochemists began to study the folding of oligomeric proteins or of larger proteins that consist of multiple domains, it became apparent that the hydrophobic interactions are not only important in stabilizing the folded conformation, but may also have a detrimental effect.^[1] During early folding stages, many proteins form intermediates that display a considerable amount of hydrophobic surface. Protein mole-

cules can associate nonspecifically through these hydrophobic patches and ultimately aggregate. Since aggregation is a second- or higher-order reaction, protein concentration plays an important role in determining whether folding to the native state or nonspecific aggregation will predominate.^[17] For a given protein, folding *in vitro* can often be improved by optimizing the experimental conditions, including protein concentration, temperature, and pH among others.

1.2. Protein Folding In Vivo

In contrast to the situation *in vitro*, all proteins have to fold under the same set of conditions in a living cell. These conditions seem to be counterproductive for efficient folding, mainly because of the high temperature and the large number of non-native proteins present. Given the circumstances, it seems surprising that cells are usually devoid of aggregated proteins. There are two possible explanations for this observation. First, aggregation does occur *in vivo*, but its products are rapidly removed by cellular proteases. This would imply that cells waste a lot of energy to produce proteins that never become functional. Second, cells have found a strategy of minimizing the aggregation of newly synthesized proteins in the first place. This has been achieved by complex protein machinery, the chaperones, which influence the spontaneous folding reaction of proteins, thus preventing aggregation. It is important to note that these molecular chaperones do not provide specific steric information for the folding of the target protein, but rather inhibit unproductive interactions and thus allow the protein to fold more efficiently into its native structure.

Stefan Walter was born in 1967 in Munich (Germany), and studied biochemistry at the University of Bayreuth (Germany). He obtained his Ph.D. in 1996 with Professor Franz X. Schmid in the field of protein folding and stability. Subsequently, he conducted postdoctoral studies on structural aspects of chaperone-mediated protein folding with Arthur Horwich at Yale University. In 1999 he returned to Germany and joined the Department of Organic Chemistry and Biochemistry at the Technische Universität, Munich. His current research interests lie in the areas of molecular chaperones and prion proteins.



S. Walter



J. Buchner

Johannes Buchner was born in 1960 in Ihrlersstein (Germany). He studied biology with a major in biochemistry at the University of Regensburg (Germany). He completed his Ph.D. thesis on the folding of recombinant proteins and the mechanism of molecular chaperones under the supervision of Prof. Rainer Rudolph at the Institut für Biophysik und physikalische Biochemie. His postdoctoral research under the supervision of Dr. Ira Pastan at the National Institutes of Health, Bethesda (U.S.A.) focused on immunotoxins for cancer therapy. In 1992, he accepted a position as group leader at the institute of Prof. Dr. Rainer Jaenicke, Universität Regensburg, where he received his Habilitation in biochemistry in 1995. In 1995 he was awarded a Heisenberg fellowship of the DFG. In 1997 he was offered a chair in biochemistry at the Medizinische Hochschule, Hannover (Germany). In 1998 he took up a chair in biotechnology at the Technical University in Munich, where he continues to work on molecular chaperones, and on biotechnological as well as medical aspects of protein folding.

Molecular chaperones are found in all compartments of a cell where folding or, more generally, conformational rearrangements of proteins occur. Although protein synthesis is the major source of unfolded polypeptide chains, other processes can generate unfolded proteins as well. At non-physiological high temperatures or in the presence of certain chemicals, proteins can become structurally labile and may even unfold. Eventually, this would result in loss of function of the affected proteins and in the accumulation of protein aggregates. The cell responds to this threat by producing increasing amounts of specific protective proteins, a phenomenon referred to as *heat-shock response* or *stress response*.^[18] Many of these proteins were found to be molecular chaperones.

1.3. Functional Properties of Molecular Chaperones

The term molecular chaperone is used to describe a functionally related set of proteins. According to their molecular weight, molecular chaperones are divided into several classes or families. A cell may express multiple members of the same chaperone family. For example, the yeast *S. cerevisiae* produces 14 different versions of the chaperone Hsp70.^[19] Proteins from the same class of molecular chaperones often show a significant amount of sequence homology and are structurally and functionally related, whereas there are hardly any homologies between chaperones from different families. Despite this diversity, however, most molecular chaperones share common functional features.

1.3.1. Binding to Proteins That Expose Hydrophobic Surfaces

The principal property of any molecular chaperone clearly is its ability to bind unfolded or partially folded polypeptides. During the early stages of folding (Figure 1, I_{uc}) or when misfolding occurs, the hydrophobic residues of a protein are partially solvent accessible and thus render it vulnerable to aggregation. Association of these hydrophobic protein species with molecular chaperones efficiently suppresses aggregation. The low specificity of the hydrophobic interaction and the conformational flexibility of folding intermediates ensures that chaperones act promiscuously: they bind to a large variety of polypeptides that differ widely in amino acid sequence and in conformation. However, since most native proteins and many late folding intermediates (Figure 1, I_c and N) do not have hydrophobic patches, they are no longer substrates for molecular chaperones.

1.3.2. Conformational Changes of Target Proteins

In general, molecular chaperones induce conformational changes in their target proteins. One example is the controlled unfolding of a protein substrate. This unfolding activity establishes a link between chaperones and the cellular protein degradation system. Unfolding may also be of importance in protein folding (see Section 2.1.6). The formation of non-native contacts can lead to misfolded species that are trapped

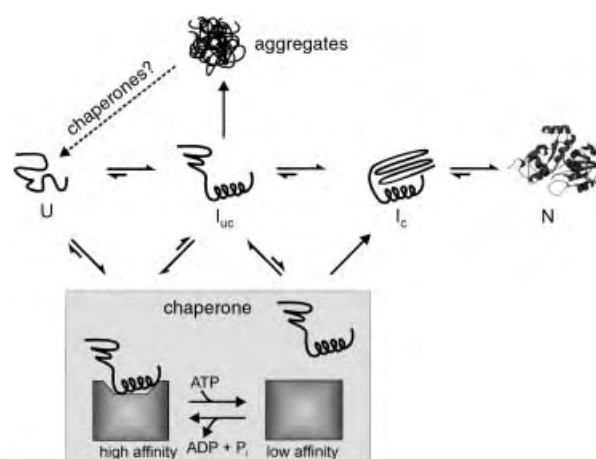


Figure 1. Chaperone-assisted protein folding. Protein biosynthesis as well as cellular stress results in the formation of unfolded polypeptides (U). These molecules fold via several intermediates (I_{uc} , I_c) with increasing structure complexity, until they reach the native, functional state (N). Some intermediates (I_{uc}) may expose hydrophobic surfaces that render them susceptible to aggregation. This reaction was thought to be irreversible, but recent results indicate that some chaperones may resolubilize aggregates. Molecular chaperones interfere with the deleterious process of aggregation by binding to species I_{uc} and U. This association not only blocks the hydrophobic patches on the bound polypeptides, but also decreases the concentration of aggregation-prone molecules, thereby slowing down aggregation. In many cases, an ATP-mediated conformation change in the chaperone triggers the dissociation of the bound polypeptide. A fraction of the released molecules may fold into a committed state (I_c), which no longer requires the assistance of the chaperone, whereas the remaining uncommitted (uc) molecules rebind and participate in another chaperone cycle. Depending on the type of chaperone, conformation changes in the polypeptide may occur during its association with the chaperone.

in local energy minima.^[20] Chaperone-mediated unfolding can disrupt these non-productive interactions and offers the polypeptide a new chance to reach its native structure.

1.3.3. Controlled Release of Bound Polypeptides

Hydrophobic interactions not only contribute to the stability of the folded structure of a protein, they are also important for the stability of oligomeric proteins and protein complexes. The contact areas often contain hydrophobic residues that become buried upon association. Thus, a protein may bind to an unfolded polypeptide or suppress its aggregation without necessarily being a chaperone. What sets molecular chaperones apart from these hydrophobic “scavengers” is their ability to form defined complexes with non-native proteins and, more importantly, to release the bound polypeptide in a controlled manner. This is usually accomplished by switching to an alternate state of the chaperone with a decreased affinity for hydrophobic polypeptides (Figure 1). According to the laws of thermodynamics, a bound protein substrate will stabilize the high-affinity state of the chaperone. Therefore some source of energy is required for switching to the low-affinity state in the presence of a bound substrate. Usually, this energy comes from the hydrolysis of ATP or the interaction with other protein components of the chaperone machinery.

2. Mechanisms of Chaperone Action

Having established the general principles of assisted protein folding, we discuss the structural and functional features of selected classes of molecular chaperones in detail in the following section.

2.1. GroE

The GroE proteins of the bacterium *E. coli* are the most extensively studied molecular chaperones.^[21–24] The *groEL* and *groES* genes encode proteins of 57 kDa and 10 kDa size, respectively, which are both required for the viability of *E. coli*.^[25] Thus, at least one essential *E. coli* protein cannot fold without assistance from the GroE chaperone.

2.1.1. Structure of the GroE Chaperone

The most striking feature of GroEL is its quaternary structure, which resembles a barrel open at both ends.^[26, 27] Fourteen subunits are assembled in two seven-membered rings, which form two separate cavities with a diameter of 45 Å (Figures 2A and B). The GroEL subunits can be dissected into three domains. The equatorial domains comprise the center part of the barrel. They bind and hydrolyze ATP and mediate all the contacts between the two rings and most of the contacts between the subunits of the same ring. The apical domains are located on the outer rims of the barrel and are responsible for binding the protein substrates and the co-chaperone GroES. The equatorial and the apical domains are connected by intermediate domains, which serve as mobile hinges that permit large structural rearrangements during the functional cycle of GroE.

The co-chaperone GroES is a dome-shaped ring-structure with a diameter of 75 Å and consists of seven subunits.^[28] An important feature of GroES is the so-called mobile loop, a stretch of 16 amino acids which mediates binding to GroEL.^[29, 30] Binding of GroES occurs at the ends of the GroEL barrel (Figure 2A), and is dependent on the presence of nucleotides, that is, ADP or ATP must be bound to the equatorial domains of the respective GroEL ring.^[31] Two types of complexes between GroES and GroEL, which differ in their stoichiometry and were aptly named “bullets” and “footballs”, have been described in the literature.^[32–36] In “bullets”, only one of the GroEL rings is associated with GroES (as in Figures 2A and B), whereas in “footballs” both GroEL rings are capped with GroES to form an apparently symmetrical particle. In the presence of ADP, “bullets” seem to be the predominant species, whereas both “footballs” and “bullets” are observed in the presence of ATP.

GroEL belongs to the family of Hsp60 chaperones, also termed “chaperonins”. For reasons of function and homology, members of this class can be divided into two groups. Group I chaperonins, such as GroEL, consist of seven subunits per ring and require a co-chaperone such as GroES. They are found in eubacteria and in the mitochondria and the chloroplasts of eukaryotic cells. Group II chaperonins consist of eight or nine subunits per ring and do not cooperate with a partner

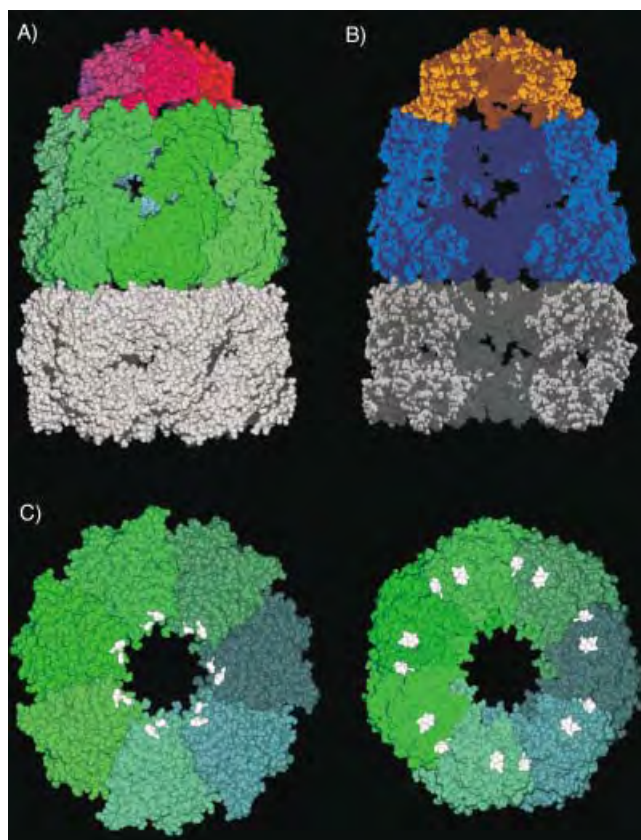


Figure 2. Structure of the GroE chaperone from *E. coli*, determined by X-ray crystallography.^[26, 27] A) Side-view of an asymmetric GroE “bullet” complex, which consists of a GroEL double-ring and a GroES single-ring. The distal GroEL ring is shown in gray, the seven subunits of the proximal GroEL ring are shown in shades of green. GroES (red) binds to the top of the proximal ring. B) Cross-section of a GroE “bullet”. Each GroEL ring encloses a cavity that serves as a folding compartment for a polypeptide substrate. Some residues of the equatorial domains have not been resolved in the crystal structure, thus giving the (wrong) impression that the two cavities are contiguous. Binding of GroES to the top GroEL ring blocks the access to the upper cavity and concomitantly induces a movement of the apical domains. The diameter of the proximal cavity increases from 45 Å to 80 Å, and its height from 73 Å to 85 Å. C) Changes in the GroEL structure upon binding of GroES. Left: the seven subunits that make up one ring of GroEL are shown in shades of green and blue. The hydrophobic amino acids in the apical domains that have been identified as important for binding the polypeptides and GroES are shown in white.^[40] In the absence of GroES, these residues coat the inside of the central cavity and account for the high affinity for unfolded polypeptides of this state. Right: upon binding of GroES, the apical domains rotate outwards by ~90°. The hydrophobic patches become buried in the subunit interfaces, thus rendering the inner surface of the cavity mainly hydrophilic and causing the release of the bound polypeptide.

chaperone. They are found in the cytosol of archaea and eukaryotes. Relative to the group I chaperonins, our molecular understanding of the group II chaperonins is limited. One of the many questions that remain to be answered is whether their substrate specificity is as broad as that observed for GroEL.^[37, 38]

2.1.2. Polypeptide Binding to GroEL

GroEL recognizes a polypeptide as a potential substrate by virtue of exposed hydrophobic surfaces, which are character-

istic for unfolded and misfolded proteins. The dominance of hydrophobic interactions in polypeptide binding has been demonstrated by determining the thermodynamic properties of the binding reaction.^[39] The protein-binding site on GroEL was identified by mutational analysis,^[40] and more recently by the X-ray crystal structures of the isolated apical domain^[41] and of a complex between GroEL and a hydrophobic peptide.^[42] The peptide binds into a hydrophobic groove around the opening of the central cavity (Figure 2C). The high plasticity of the binding site allows it to undergo subtle structural rearrangements, thereby providing an optimized binding surface for individual substrates. Since the partially folded substrate is flexible as well, it is very likely that both the substrate and the apical domains will undergo structural rearrangements upon association.^[43] This explains why GroEL can bind to a wide range of partially folded proteins.

The structures of various substrate proteins have been characterized while bound to GroEL. It appears that GroEL is capable of interacting with a host of different conformations, ranging from largely unfolded polypeptides to highly structured stable folding intermediates.^[44–46] How can this structural heterogeneity be explained? From a thermodynamic point of view, there is a competition for the protein substrate between folding (i.e. formation of structure) on the one hand, and binding to GroEL on the other hand, because both are driven by the hydrophobic effect. In the case of folding, the hydrophobic residues become shielded from the solvent by forming a hydrophobic core in the protein. In the case of binding, shielding is achieved by interaction with the hydrophobic groove of the apical domains of GroEL.

For a single residue in a polypeptide substrate these options are mutually exclusive, but not necessarily for the whole protein. The structure(s) of the bound polypeptide might reflect an energy minimum that is determined by the relative size of two ΔG values, one for folding and one for binding. In essence, GroEL puts no restriction on the structure of the bound protein, as long as there is enough hydrophobic surface to interact with. This is different from Hsp70 (see below), in which the channel-like architecture of the binding site requires a locally stretched conformation of the bound polypeptide.^[47]

2.1.3. Interaction between GroEL and GroES

A key element in the functional cycle of GroE is the interaction between the two partner chaperones. Binding of the GroES co-chaperone induces major structural changes in the GroEL particle.^[27, 48] First, GroES serves as a lid that closes the cavity of the ring it is bound to, thereby encapsulating a polypeptide attached to the same ring. Second, it induces a rigid body movement of the apical domains in GroEL that completely changes the nature of the cavity: the hydrophobic patches in the apical domains which are responsible for polypeptide binding are replaced by largely polar residues (Figure 2C). Concomitantly, the affinity for hydrophobic polypeptides strongly decreases, and the bound substrate is released into the closed cavity.^[49, 50] Third, this domain movement increases the volume of the cavity from $\sim 85\,000\text{ \AA}^3$ to $\sim 175\,000\text{ \AA}^3$. This provides sufficient

space for the released polypeptide to undergo the conformation rearrangements required for reaching its native state. Thus, binding of GroES serves as a molecular switch that puts the chaperone from binding mode into folding mode: it stimulates the release of the bound protein into an environment that favors productive folding.^[49, 50] Because of the finite cavity volume, however, GroE-assisted folding is restricted to proteins smaller than 60 kDa.^[51] Interestingly, a protein that requires both GroEL and GroES for its folding has been identified, although its size (82 kDa) makes it too big to fit in the cavity.^[52] In this special case, however, the mechanism of GroE-mediated folding seems to be different.^[53]

2.1.4. ATP Hydrolysis by GroEL and Substrate Release

After its (partial) folding inside GroE, the protein has to exit the cavity and exert its biological function in the cell. But how can it leave while GroES is blocking its way out? Although the GroEL/GroES complex is very stable ($K_d \sim 1\text{ nM}$), the ATPase serves as a built-in timer that controls the discharge of GroES. The seven molecules of ATP bound to the *cis* ring, that is, the ring associated with GroES and the folding polypeptide (Figure 3), are hydrolyzed at a rate of $0.25\text{--}0.5\text{ min}^{-1}$.^[54, 55] This induces a conformation change in

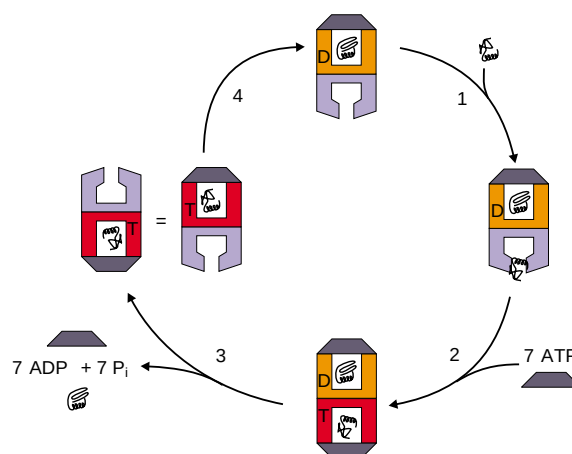


Figure 3. GroE chaperone cycle. Although GroEL is composed of two rings, the functional cycle is best described on the level of single rings, which represent the operational units of the chaperone. Although both rings are active at the same time, they are in different phases of the cycle. The processing of an individual substrate polypeptide requires two revolutions of the GroE cycle, during which the polypeptide remains associated with the same GroEL ring. For graphical reasons, however, the orientation of the GroEL molecule is reversed after step 3 (i.e. the polypeptide does not “move” to the top ring as shown). GroE-assisted folding can be dissected into 3 steps: capture, encapsulation/folding, and release. During capture (step 1; D = ADP), a hydrophobic polypeptide is prevented from aggregation by binding to GroEL. The acceptor ring (lilac) is nucleotide-free and therefore has a high affinity for the polypeptide. Binding of ATP (T) and GroES to this ring (step 2) induces a set of structural changes in GroEL (top ring, orange). Most importantly, the affinity for the bound polypeptide is decreased and it is released into the closed cavity where it starts to fold. Subsequent hydrolysis of ATP (step 4) induces a second conformational change in GroEL (top ring, orange), which allows the *trans* ring (bottom ring, lilac) to bind polypeptide and start a new cycle. Once ATP binds to the *trans* ring (red), GroES is displaced from the *cis* ring (orange), and the substrate polypeptide is released (step 3).

GroEL that increases the affinity of the *trans* ring for ATP.^[56] Binding of ATP to the *trans* ring triggers the release of the GroES in the *cis* ring and thus allows the encapsulated protein to exit the cavity.^[57]

2.1.5. The Functional Cycle of GroE

The functional cycle of GroE-assisted protein folding (Figure 3) can be divided into three steps: capture, folding, and release.^[23] During the capture phase, a polypeptide substrate is bound to the apical domains of one GroEL ring. In the second step, binding of Mg/ATP and GroES to the same ring creates a folding-active *cis* complex by inducing major conformational changes in the GroEL tetradecamer. The polypeptide is discharged into the protected environment of the *cis* cavity and starts to fold. After 15–30 s, the ATP bound to the *cis* ring is hydrolyzed, and a second conformational change primes GroEL for the release of GroES by binding ATP to the *trans* ring. The polypeptide is released from the cavity, irrespective of its folding state.

The input of energy associated with ATP hydrolysis is used to maintain the balance sheet of the chaperone cycle. Each individual step, that is, binding of polypeptide, GroES, and ATP, is an exergonic and therefore irreversible reaction, which drives the cycle in one direction. Since the starting point in a cycle is identical to the end point, there must be an energy source to compensate for this loss of energy.

2.1.6. Unfolding of Polypeptides by GroE

An important question is how GroEL promotes the folding of proteins that are trapped in non-native conformations, a situation referred to as misfolding. It is assumed that GroEL is capable of partially unfolding these proteins, thereby setting them back on the right track to the native state.

Data from different laboratories indicate that there are several potential mechanisms that GroEL could utilize to unfold a protein. The most simple model, thermodynamic coupling, is based on the aforementioned competition between binding and folding.^[58] Since binding to GroEL requires a polypeptide to expose hydrophobic surfaces, and the amount of exposed hydrophobic surface generally decreases with the degree of folding, GroEL will preferentially bind to more unfolded conformations of a protein. Provided there is a rapid equilibrium between the various conformations of the polypeptide, GroEL will effectively unfold the protein. This capability of GroEL has been demonstrated for a variety of relatively small proteins.^[59]

The coupling mechanism, however, has one important shortcoming. It would not allow a polypeptide to escape from a kinetic trap on its folding pathway, because, according to this model, all unfolding reactions occur in free solution at their intrinsic rates. This problem may be solved by an alternative mechanism for GroEL-mediated unfolding. A stable, compact folding intermediate of the enzyme Rubisco was shown to bind to GroEL without any major structural changes. But upon addition of ATP and GroES, this intermediate became transiently unfolded,^[60] likely as a result of the movements of the apical domains which occur upon GroES binding (Fig-

ure 2C). This may exert a mechanical stress on the bound protein, thereby virtually tearing its structure apart. Importantly, this mechanism requires that the polypeptide is bound to multiple apical domains simultaneously.^[61] Active unfolding, however, could not yet be observed with other stringent substrate proteins of GroE. In the case of malate dehydrogenase (MDH), no significant structural changes are observed when the MDH/GroEL complex dissociates upon binding of GroES.^[45]

2.1.7. Folding Inside the Chaperone

Once GroES is bound, the substrate is released into the protected environment of the *cis* cavity. This gives the protein the opportunity to fold without interference from other folding polypeptides, since GroES blocks the entry to the cavity, and unfavorable side reactions such as aggregation can therefore not occur. This situation is often referred to as folding in “infinite dilution” or folding in the “Anfinsen cage”. Monomeric proteins might reach the native state during these 15–30 s, provided their folding is sufficiently fast. Alternatively, they might fold into a committed state, in which they no longer require the assistance of the GroE chaperone although they have not reached the native structure yet (Figure 1). For an oligomeric protein whose native state involves the assembly of several polypeptide chains, this committed state represents the obligatory exit point from the chaperone cycle, because further encapsulation would actually block the pathway to the native protein.^[45, 62]

Proteins that fold more slowly than the time taken for a chaperone cycle are assumed to undergo kinetic partitioning after dissociation from GroE. A fraction of the protein molecules will have reached either the native state or the committed state and will therefore no longer be a substrate for assisted folding.^[63] The remaining molecules have the chance to rebind to GroEL and participate in another chaperone cycle. As discussed above, it is possible that this step includes structural rearrangements such as unfolding of kinetically trapped species that might have formed.

An open question is whether the walls of the cavity have any effect on the folding protein, that is, whether the energy landscape that describes the folding pathway is altered by the steric restraints and the complex chemical composition of the local environment. An investigation of such an effect would require a comparison between folding inside GroEL and folding in free solution, which is possible only for proteins whose folding is not dependent on GroE.

How long is the optimal cycle time for GroE-assisted folding? Generally, longer cycle times mean that GroEL hydrolyzes less ATP per second and therefore consumes less energy. It also means that, on average, a polypeptide would spend more time in the folding cage. This would have two consequences: more GroEL molecules would be needed per cell to provide the required chaperone capacity, and it would slow the folding of fast-folding proteins. Even worse, subunits of some oligomeric proteins may adopt a conformation that is no longer capable of assembling if kept in the “Anfinsen cage” for too long.^[64] On the other hand, if the cycle is too fast, the chaperone system may become less efficient. Faster cycling

leads to an increase in energy consumption, but not necessarily to improved folding yields.

To accomplish its task as a molecular chaperone, GroEL must be capable of binding to a large variety of unfolded, misfolded, and partially folded polypeptides. Experiments with denatured cell extracts have demonstrated that about 40% of the *E. coli* proteins can interact with GroEL.^[65] However, it is unlikely that GroE participates in the folding of all these proteins, because the cellular concentration of GroEL ($\sim 1 \mu\text{M}$) is simply too small for that purpose.^[66] A number of *E. coli* proteins that interact with GroEL have been identified recently,^[67] but it is still not clear how many of them are stringently dependent on GroEL in their folding.

2.2. The Hsp70 System

The Hsp70 proteins constitute the central part of an ubiquitous chaperone system that is present in most compartments of eukaryotic cells, in eubacteria, and in many archaea. As in the case of the GroE proteins, the most extensively studied representative of this chaperone group, the DnaK protein, is from the bacterium *E. coli*. Hsp70 proteins are involved in a wide range of cellular processes, including protein folding and degradation of unstable proteins (for a discussion, see ref.^[68]). The common function of Hsp70 in these processes appears to be the binding of short hydrophobic segments in partially folded polypeptides, thereby preventing aggregation and arresting the folding process.^[19, 69]

DnaK and many other Hsp70 chaperones interact in vivo with two classes of partner proteins that regulate critical steps of its functional cycle, similar to the cooperation between GroEL and GroES: the Hsp40 and the GrpE proteins. Furthermore, additional partner proteins have been identified in the past years, especially in eukaryotic cells, and some of them link Hsp70 to other chaperone systems (see Section 2.3).

2.2.1. Structural and Functional Properties of Hsp70

Hsp70 is comprised of two functional entities: an N-terminal ATPase domain, and a smaller C-terminal peptide-binding domain. The crystal structures of both the ATPase domain and the peptide-binding domain of DnaK have been determined.^[70–72] The ATPase domain of Hsp70 (Figure 4A) is comprised of two subdomains separated by a cleft that contains the nucleotide-binding site.^[73] The nature of the bound nucleotide determines the peptide-binding properties of the C-terminal domain. In the ATP state, peptide substrates bind and dissociate very rapidly albeit with low affinity.^[74] With no nucleotide or ADP bound to the N-terminal domain, the rates of peptide binding and dissociation decrease by more than two orders of magnitude, and the affinity increases significantly. ATP hydrolysis thus serves as a molecular switch between two states of Hsp70, characterized by high dynamics/low affinity or low dynamics/high affinity. Since the structure of full-length Hsp70 has not been determined yet, we have no direct information on how communication between nucleotide binding and peptide binding occurs at a molecular level. However, the X-ray crystal structure of the peptide binding

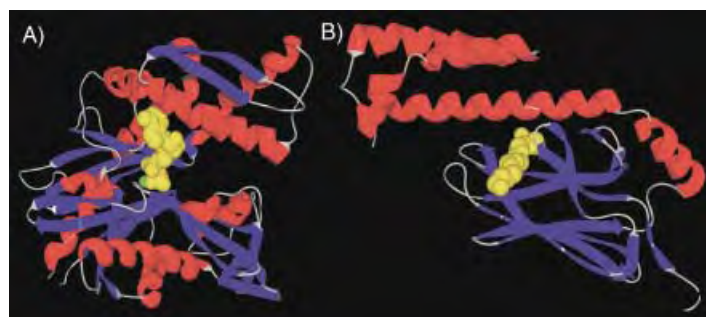


Figure 4. Structure of the DnaK chaperone from *E. coli*. A) Crystal structure of the nucleotide-binding domain of DnaK complexed with ADP.^[71] The nucleotide (yellow) and a magnesium ion (green) are bound in a deep, solvent-inaccessible crevice formed by two subdomains of the protein. The structure is very similar to that of two other ATP-binding proteins, hexokinase and actin. B) Crystal structure of the peptide-binding domain of DnaK complexed with a heptameric peptide.^[72] The peptide-binding site consists of a hydrophobic groove that is located in a subdomain formed by eight antiparallel β -strands (blue). The peptide NRLLLTG (yellow; only the backbone atoms are shown) binds to this groove in an extended conformation and is locked in place by an all-helical subdomain (red). Presumably, this conformation represents the high-affinity state of Hsp70.

domain of DnaK co-crystallized with a heptapeptide bound to its active site provides insight into how this communication might work.^[72]

2.2.2. Peptide Binding by Hsp70

The peptide-binding domain (Figure 4B) consists of two structural units, a β sandwich with a hydrophobic groove on its upper side, and a α -helical domain that sits on top of it. The peptide substrate is bound to the groove in a stretched backbone conformation (see Figure 4B). It is held in place by hydrophobic interactions and hydrogen bonds between the peptide and the β sandwich. The α -helical domain covers the top of the cleft and traps the peptide in the binding site. It is very likely that this “closed” structure corresponds to the ADP state of Hsp70, since it would readily explain the high peptide affinity and the slow exchange kinetics. How could binding of ATP to the N-terminal domain of Hsp70 increase the dynamics of peptide binding? The current model assumes that ATP binding induces a conformational change in the chaperone that removes the helical lid from the peptide binding groove, thus making it accessible to solvent.^[47]

Analyses with peptide libraries have shown that Hsp70 preferentially binds to peptides that contain hydrophobic residues.^[75–77] In proteins, this type of sequence is mainly found in the core of the folded structure, or in subunit interfaces.^[78] Furthermore, the topology of the peptide-binding site in Hsp70 requires that the bound segment is separated from the rest of the protein substrate by $\sim 10 \text{ \AA}$. This implies that the portion of the substrate that is bound to Hsp70 must be considerably unfolded and highly flexible.

Besides the specificity of polypeptide binding, its kinetics are also of importance. Aggregation is a relatively fast process that occurs on a timescale of seconds. To compete with it, complex formation between an unfolded polypeptide and Hsp70 must be equally fast. In the nucleotide-free state,

association rate constants for peptide substrates were in the range of $10-100\text{ M}^{-1}\text{ s}^{-1}$.^[79] If a cellular concentration of $10\text{ }\mu\text{M}$ is assumed for an unfolded polypeptide, complex formation would take at least several minutes. It would thus be too slow to prevent a substrate from aggregating. In the “open” ATP-bound state of Hsp70, binding kinetics for peptides are accelerated by at least one order of magnitude. However, the capture of a polypeptide requires the conversion of this labile Hsp70/ATP/polypeptide complex into the more stable Hsp70/ADP/polypeptide form by hydrolysis of the bound ATP. But this reaction, which occurs at a rate of only $\sim 0.1\text{ min}^{-1}$, is again too slow to compete with aggregation. The somewhat puzzling conclusion is that for kinetic reasons Hsp70 proteins should not be very potent suppressors of aggregation, a fact that is illustrated by the experimental observation that DnaK alone is not efficient in preventing the aggregation of non-native proteins.^[80, 81] The solution to this problem is provided by the co-chaperones Hsp40 and GrpE, and highlights their importance in the Hsp70 system.

2.2.3. Partner Proteins of Hsp70—Modulation of the Functional Cycle

Hsp40 belongs to a diverse class of proteins that consist of multiple functional domains. One of the domains, the ~ 75 -amino-acid J domain, is conserved in all Hsp40 chaperones. Mutational analysis revealed that this domain is essential for the interaction between Hsp40 and Hsp70.^[82] Its name is derived from DnaJ, the Hsp40 protein from *E. coli* that cooperates with DnaK. The most important features of Hsp40 are that it binds to peptides, and that it stimulates ATP hydrolysis of Hsp70.^[83] A current model of how Hsp40 and Hsp70 cooperate (Figure 5) assumes that a polypeptide

substrate first binds to Hsp40.^[81] The Hsp40/protein complex then associates with Hsp70/ATP, the protein substrate is transferred to the open peptide-binding cleft of Hsp70, and locked in by the subsequent Hsp40-stimulated hydrolysis of ATP. The functional cycle of Hsp70 is completed by the exchange of ADP for ATP, which shifts the chaperone back into its dynamic mode and allows the bound polypeptide to dissociate.

In the presence of Hsp40, ATP-hydrolysis is accelerated and may no longer be the rate-limiting step. Thus, it does not come as a surprise that the second potentially slow reaction of the cycle, nucleotide exchange, can also be stimulated. The co-chaperone responsible for this is GrpE,^[84] which interacts stably with nucleotide-free Hsp70, but not with nucleotide-bound Hsp70. Accordingly, GrpE decreases the affinity of Hsp70 for nucleotides. Facilitated nucleotide exchange appears to be a two-step process (Figure 5). In the first step, GrpE binds to Hsp70 and thus displaces the bound ADP. Subsequently, the binding of ATP to Hsp70 stimulates the release of GrpE.^[85, 86] The crystal structure of GrpE bound to the nucleotide-free ATPase domain of DnaK gives us some hints as to why GrpE decreases the affinity of DnaK for nucleotides.^[71] The nucleotide-binding pocket in the complex is more open than in free DnaK, and therefore less interactions between the nucleotide and the protein are possible.

To date, there is no experimental evidence that Hsp70 chaperones can actively induce conformational changes in their target proteins as has been shown for other molecular chaperones. Furthermore, unlike GroEL, Hsp70 does not provide a favorable micro-environment for protein folding. Rather, Hsp70 seems to serve as a general acceptor for unfolded polypeptides generated by protein biosynthesis or by cellular unfolding processes. The interaction of these target proteins with Hsp70 prevents aggregation and arrests folding. What happens after their release from Hsp70 may depend on the nature of the polypeptide and on the cellular context. Some proteins may fold spontaneously into their native structure, while others may be transferred to more specialized chaperone machines such as GroE or Hsp90, or to systems involved in protein transport or degradation.

2.3. The Hsp90 Chaperone System

Eukaryotes in particular have evolved an additional chaperone machinery, Hsp90, which is far more complex than both GroE and Hsp70. First, it includes the Hsp70 system, at least during part of the chaperone cycle, and second, it comprises a large number of cofactors. More than a dozen have been identified so far.

What makes this chaperone system unique is that relative to the other chaperones, already a large number of client proteins have been identified which depend on Hsp90 to reach their functional conformation under physiological conditions. This suggests that stable complexes that allow isolation are formed between Hsp90 and its client proteins. A striking example, which highlights the influence of Hsp90 on protein folding, is the case of src kinase. This protein is an

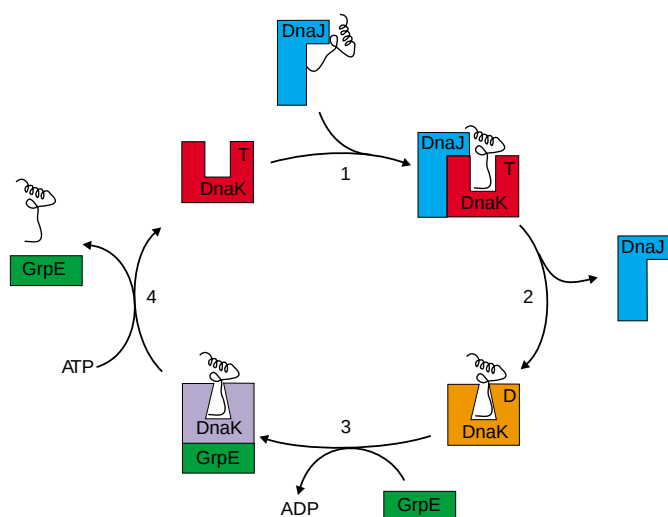


Figure 5. *E. coli* DnaK chaperone cycle. A largely unfolded polypeptide substrate (black ribbon) is captured by the co-chaperone DnaJ (blue). Upon complex formation with DnaK (red), the substrate is transferred from DnaJ to the peptide-binding site of DnaK (step 1). DnaJ-stimulated hydrolysis of ATP (T) closes the binding site (orange conformation of DnaK) and locks in the substrate, thus forming a stable protein/DnaK complex (step 2). After the dissociation of DnaJ, the bound ADP (D) is displaced by the nucleotide exchange factor GrpE, shown in green (3). Subsequent binding of ATP to DnaK releases GrpE and induces a conformational change that opens the peptide binding site (4). The polypeptide can dissociate.

important player in the regulation of the cell cycle and therefore constitutes an interesting target for therapeutic intervention. Screens for natural substances that inhibit src function *in vivo* led to the selection of the ansamycin geldanamycin.^[87] However, subsequent analysis showed that this potential inhibitor of src binds to Hsp90 with high affinity and high specificity.^[88] This interaction inactivates Hsp90 which in turn leads to decreased levels of active src kinase.

The number of proteins that require the Hsp90 system for reaching their functional conformation is growing steadily.^[89] But at the moment it is not known what common feature—a sequence motif or a specific structural element—is the basis for their interaction with Hsp90. Many of the substrate proteins of Hsp90 are regulatory proteins or perform key functions in proliferation. One may speculate that the Hsp90 dependence of their activity could enable an additional level of regulation.^[90]

How does Hsp90 fulfill its task? Results from *in vivo* experiments suggest that the target polypeptide passes through several Hsp90 complexes that differ in the composition of partner proteins.^[91] The conformational changes of the target protein that occur during this passage are completely unknown. In an enigmatic way, the acquisition of the functional conformation of the target protein is promoted through the interactions with different Hsp90 complexes.

2.3.1. Structural and Functional Properties of Hsp90

Hsp90 is an elongated homodimer with a dissociation constant of ~ 60 nM.^[92, 93] The dimerization site is located in the C-terminal part of the protein.^[92, 94] The three-dimensional structure of the N-terminal domain of Hsp90 (amino acids 1–215) has been solved by X-ray crystallography (Figure 6).^[95, 96] This domain exhibits a novel fold, which consists of a β sheet

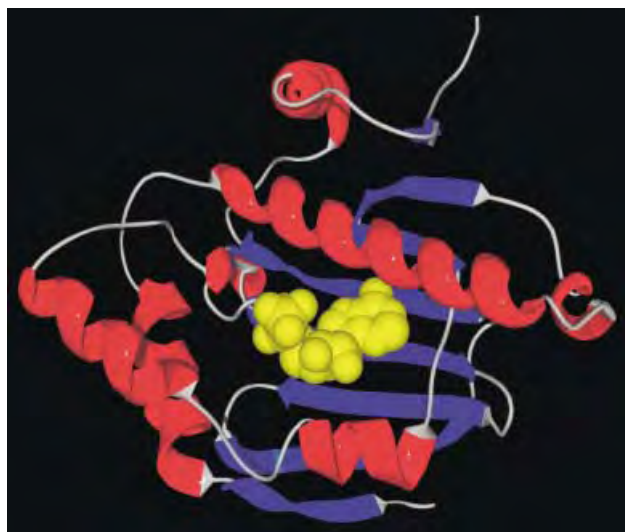


Figure 6. Structure of the N-terminal ATP-binding domain of yeast Hsp90 complexed with ADP.^[97] The domain consists of a twisted eight-stranded β -sheet with a cluster of α -helices arranged on top of it. The nucleotide (yellow) is bound in an unusual kinked conformation in a deep pocket formed by the surrounding helices and loops. This pocket also constitutes the binding site of the antitumor drug geldanamycin.^[95]

and helices arranged on top of it. It was later found that this domain contains the ATP-binding pocket.^[97] ATP is bound in an unusually kinked conformation: the adenosine ring and the ribose unit are buried in the interior of the binding pocket and the phosphate groups point to the surface. Like the GroEL and Hsp70 chaperones, Hsp90 is a weak ATPase.^[98, 99] Hsp90 from the baker's yeast *S. cerevisiae* hydrolyzes ~ 0.3 ATP min⁻¹ at the physiological temperature of the organism. ATP hydrolysis seems to be of crucial importance for Hsp90 function *in vivo*, because mutant proteins that do not hydrolyze ATP do not support the functions of Hsp90 essential for viability.^[99, 100] Recent findings suggest that the ATPase cycle is coupled to large conformational changes in the Hsp90 dimer.^[101, 102] Kinetic analysis of the ATPase reaction showed that regions outside the ATP-binding domain are important for efficient hydrolysis. It is therefore reasonable to assume that once ATP is bound, the N-terminal domain interacts with other parts of the Hsp90 molecule which may include an acceptor for the γ -phosphate group of ATP.^[102] In addition, the two N-terminal domains of the Hsp90 dimer interact in the presence of ATP.^[101] This interaction is required for coordinated and efficient ATP hydrolysis.^[93] How these ATP-induced interactions affect the conformation of the client proteins remains to be seen.

Two consequences of the ATPase cycle can be envisioned which highlight the concept of molecular chaperones as machines: 1) The movements of domains may affect the accessibility of binding sites for nonnative proteins, similar to what has been observed for GroEL. Fragmentation studies have suggested that Hsp90 contains two binding sites for nonnative proteins which differ in their specificities.^[98, 103] It may well be that these sites, which are located in different parts of the protein, cooperate in an ATP-regulated manner. 2) ATP-induced conformational changes in Hsp90 may affect the interaction with specific cofactors or partner proteins. This implies that the Hsp90 chaperone cycle is driven and regulated by ATP hydrolysis. Since the hydrolysis reaction and the formation of the different Hsp90 complexes required for the activation of client proteins occur on the same timescale,^[104] this may well be the case.

2.3.2. Partner Proteins of Hsp90

So far, only limited information is available on what factors regulate the association of Hsp90 with its numerous partner proteins. More importantly, the function of these cofactors is also largely unknown. Some of the partner proteins contain “docking modules”, the so-called tetratricopeptide repeat (TPR) motifs, which consist of arrays of helices that form a groove in which an extended peptide sequence can bind.^[105] The interacting peptide sequences have been found in the C-terminal ends of Hsp90 and Hsp70.^[106] Hop/Sti1, one of the partner proteins of Hsp90 and of central importance for the Hsp90 cycle, consists mainly of TPR motifs, in agreement with its function of bringing the Hsp70 and Hsp90 chaperones together (cf. Figure 7).^[107] In addition, Hop/Sti1 inhibits the ATPase of Hsp90 upon binding.^[108]

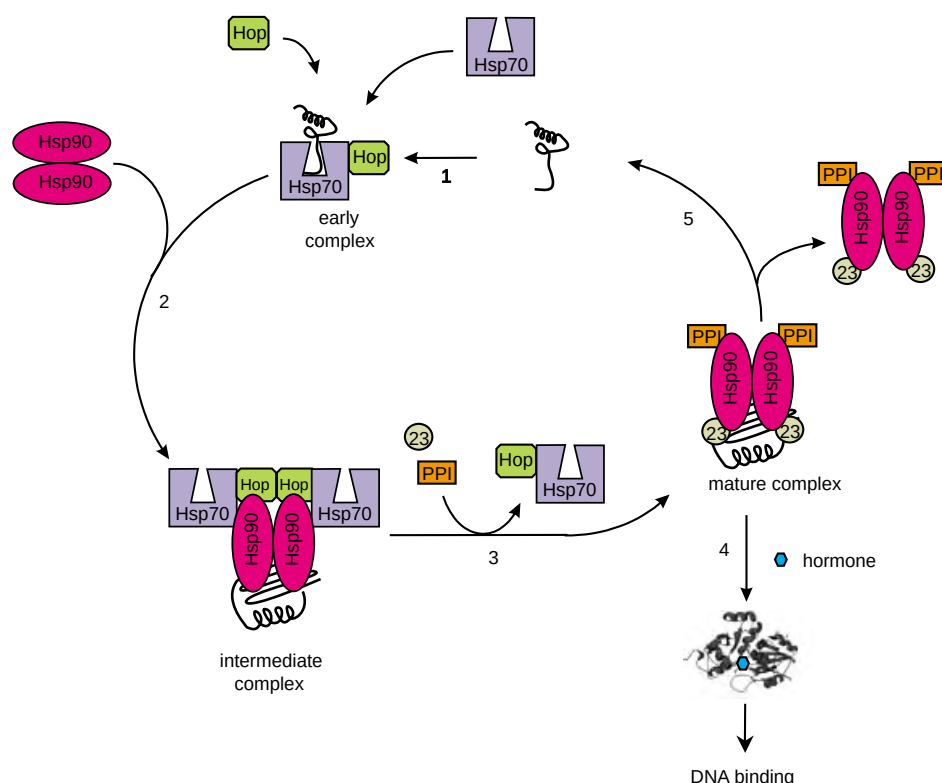


Figure 7. Hsp90 chaperone system for a steroid hormone receptor (SHR). The involvement of cofactors may change depending on the target protein. In the case of SHR, an inactive conformation of the receptor is captured by the molecular chaperone Hsp70 (step 1). The co-chaperone Hop is recruited to establish a physical connection between Hsp70 and Hsp90. Presumably, ATP hydrolysis by Hsp70 releases the bound SHR and transfers it to the Hsp90 dimer, thus resulting in the formation of the intermediate complex (step 2). Transition to the mature complex is mediated by the replacement of both Hsp70 and Hop with large prolyl isomerases (PPI) and another helper protein (p23) (step 3). Upon binding of its hormone ligand, the SHR is released from the mature complex, the receptor switches to its active conformation and migrates to the nucleus (step 4). In the absence of a hormone ligand, the receptor protein may participate in another cycle (step 5).

Other Hsp90 cofactors belong to the class of peptidyl-prolyl isomerases (PPIases), enzymes that catalyze the *cis/trans* isomerization of prolyl-peptide bonds in proteins.^[109, 110] Single-domain PPIases are involved in signal transduction and protein folding *in vivo*. In yeast there are two large Hsp90-associated PPIases, whereas in higher eukaryotes three different isoforms have been identified. In addition to the PPIase domains, they all have other domains. Interestingly, the Hsp90-associated PPIases also contain TPR motifs. It is presently unclear what the function of these enzymes is in the Hsp90 complex and how they are selected for incorporation into the Hsp90 complex. There is some evidence that the bound client protein is involved in this process.^[111] Because of their enzymatic activity one may speculate that catalysis of *cis/trans* isomerization is also important in the context of the Hsp90 complex. It has been demonstrated already that all Hsp90-associated prolyl isomerases and a small Hsp90-binding protein (p23) share the ability to bind selectively non-native proteins *in vitro*,^[112–115] which suggests that these proteins may be in direct contact with the client protein in the Hsp90 complex. Thus the Hsp90 system is a highly dynamic, reversibly assembling molecular machine with moving parts.

2.3.3. Regulation of Protein Conformation by Hsp90

How does Hsp90 affect the folding of other proteins? At present, it seems that under physiological conditions Hsp90 does not play a major general role in the *de novo* folding of proteins.^[116] However it is of critical importance for the folding of a number of proteins that are involved in key regulatory processes. There is some indirect evidence that these target proteins exist in metastable conformations. In the case of steroid hormone receptors, the ligands form part of the hydrophobic core of the protein and thus contribute significantly to the stability of the folded structure. Hsp90 may thus be required to keep steroid hormone receptors in an open state that is capable of ligand binding (Figure 7). In the absence of the chaperone, the receptor may assume an energetically more favorable collapsed state. In a number of cases, the chaperone dependence allows an additional level of regulation for the target protein which is independent of a target-specific signal. Furthermore, association with Hsp90 may generally stabilize unstable intermediate conformations

and thus increase the conformational space that proteins can successfully explore. Regulation of conformation may be the common denominator for an otherwise structurally and functionally diverse set of Hsp90 client proteins. Moreover, it seems reasonable to assume that under stress conditions Hsp90 may interact with a larger number of unfolded proteins.

2.3.4. The Hsp90 Chaperone Cycle

For regulation of the conformation, the substrate protein has to pass through three complexes, which differ in the composition of the cofactors.^[91, 104] First, the client protein seems to be bound by Hsp70 and its cofactors (Figure 7, step 1) which then form a complex with Hop/Sti1 and Hsp90 (Figure 7, step 2). It is assumed that the non-native protein is handed over from one chaperone to the other in this step, analogous to the substrate transfer from Hsp40 to Hsp70 (Figure 5).^[117] As in all processes in which Hsp70 is involved, it is unclear what conformational consequences binding and release have for the client protein. Also, it is unknown whether binding of Hsp90 client proteins to Hsp70 has to precede binding to Hsp90. This may depend on the respective client protein. *In vitro*, Hsp90 is able to directly bind to non-

native proteins.^[90, 118] In one well-studied example, the bound protein was shown to be largely folded. On the folding trajectory this conformation seems to be rather close to the native state, with significant secondary and tertiary structure, but it lacks enzymatic activity.^[119] This is in good agreement with the proposed conformation of ligand-free steroid hormone receptors described in Section 2.3.3.

Unlike the other chaperones, the formation and dissociation of a complex between Hsp90–Hsp70–Sti1/Hop and the non-native protein is only part of the cycle. Following the association of these chaperone components with a non-native protein, Hsp70 and Sti1/Hop dissociate from Hsp90 and the cofactors p23 and one of the large PPIases associate (Figure 7, step 3).^[120] The cofactor p23 binds to Hsp90 only in the presence of ATP.^[121] However, no other factors that govern the association of the Hsp70–Hsp90 complex and the formation of the Hsp90–p23–PPIase complex are currently known. From this Hsp90–p23–PPIase complex, the non-native protein is released (at least in the case of the steroid hormone receptor) in its active conformation, which is capable of ligand binding (Figure 7, steps 4 or 5).^[122] It is reasonable to assume that conformational changes in Hsp90 govern the interaction with the different components of the chaperone machinery. Thus, the partner proteins may either monitor whether Hsp90 is loaded with substrate and regulate the progress of the cycle accordingly, or they may be directly involved in changing the conformation of the target protein bound to Hsp90.

2.4. Small Heat-Shock Proteins (sHsps)

Yet another variation on the theme of protecting proteins from irreversible aggregation by reversible interaction with specialized folding factors is represented by the small heat-shock proteins (sHsps). These proteins have been found in almost all organisms studied so far. In many organisms, several different family members are present in one compartment, thus suggesting functional diversity. In comparison to the other classes of chaperones, they show a characteristic heterogeneity in sequence and size. Their common trait is a conserved C-terminal domain, the α -crystallin domain, which refers to the most prominent family member, the eye-lens protein α -crystallin.^[123]

2.4.1. Structure

All sHsps investigated up to now form oligomeric complexes, mainly of 12 to 42 subunits. The three-dimensional structure of an archaeal sHsp was studied by X-ray crystallography and revealed a hollow sphere with openings to the inside (Figure 8).^[124] The basic building block of this oligomeric structure is a dimer, which associates further to form the sphere. The C-terminal domain of the monomer is predominantly β structured; the structure of the N-terminal domain could only partly be resolved. The reconstruction of the three-dimensional structure of the eye-lens protein α -crystallin by electron microscopy confirmed the picture of a hollow spherical structure.^[125] However, whereas the archaeal sHsp

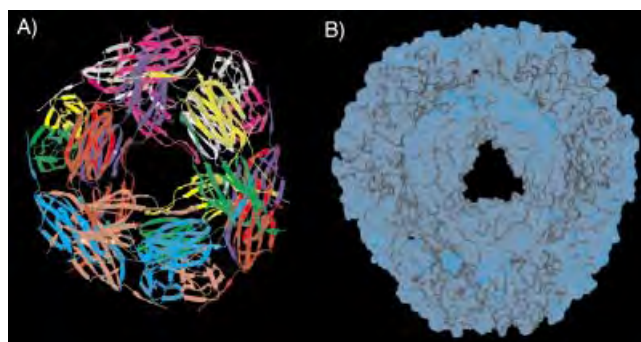


Figure 8. Structure of the small heat-shock protein from the archaeon *Methanococcus jannaschii*.^[124] A) The heat-shock protein forms a porous, hollow sphere, which consists of 24 identical subunits. The subunits are mainly β -structured. B) Cross-section. The outer diameter of the particle is ~ 120 Å, the inner diameter is ~ 65 Å, and the volume of the cavity $\sim 140\,000$ Å³. Because of its amino acid composition, the inner surface is much more hydrophobic than the outer surface.

has a rigid and well-defined quaternary structure, a range of different oligomers was detected for α -crystallin.

2.4.2. Complex Formation with Unfolded Proteins

sHsps have been included in the class of molecular chaperones because they bind specifically to unfolded proteins in vitro and prevent their aggregation.^[126, 127] Compared to the molecular chaperones discussed above, sHsps have a remarkable binding capacity. They are able to bind a large number of non-native proteins, possibly up to one target protein per subunit of the oligomeric sHsp complex.^[128] Furthermore, there seems to be no restriction on the size of proteins that can be bound.^[129]

A striking feature of the sHsps is that upon substrate binding, they form very large complexes of regular globular shape. In agreement with the lack of intermediates in the formation of substrate/chaperone complexes, this process was found to be highly cooperative.^[130] The simultaneous binding of non-native proteins seems to be a prerequisite for efficient and stable complex formation. The specificity of this reaction is further highlighted by the finding that binding can be saturated at a defined ratio of non-native protein to sHsp. The underlying mechanism is still unresolved. In the case of Hsp26, a sHsp from yeast, in vitro experiments gave insight into the regulation of the binding activity of this chaperone.^[130] At temperatures above 40 °C, the well-defined oligomeric complex dissociates into stable dimers in a completely reversible reaction. This dissociation seems to expose binding sites for non-native proteins. Remarkably, the binding of the substrate protein to the Hsp26 dimer results in the formation of large defined complexes (Figure 9). The resulting substrate/sHsp complex shows an organization that is completely different from the Hsp26 complex.

2.4.3. sHsps as Part of the Chaperone Machinery

The complexes sHsps form with non-native proteins in vitro are remarkably stable.^[128–131] Although the non-native protein is not released spontaneously, these complexes are not

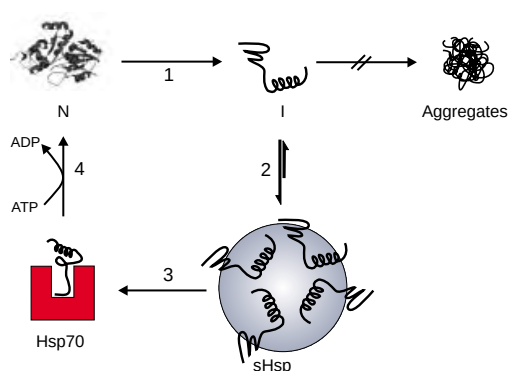


Figure 9. sHsp chaperone system for a polypeptide substrate. Under conditions of heat shock or chemical stress, some polypeptides (N) in the cell may become partially unfolded, leading to the accumulation of folding intermediates (I) (step 1). These molecules are rescued from aggregation by association with small heat-shock proteins (step 2). In the presence of Hsp70, the resulting large polypeptide/sHsp complexes can dissociate (step 3). The molecular mechanism of this stimulated release, however, is currently not known. After the transfer of the protein substrates to the Hsp70 chaperone system, the polypeptides refold in an ATP-dependent process (step 4, cf. Figure 5).

dead-end traps for the unfolded protein. As a proof of principle, it has been demonstrated that a bound enzyme can be shifted back to the native state by adding a specific ligand that stabilizes the functional conformation of the protein.^[131] However, in contrast to other chaperones, no active-release mechanism has been detected so far. Interestingly, in some organisms the expression of an sHsp and an Hsp70 chaperone is genetically linked.^[132] This and the finding that overexpression of Hsp70 has a beneficial effect on the clearance of aggregates *in vivo* suggest that sHsps may function together with other ATP-dependent members of the chaperone family.^[133] Biochemical proof for this co-operation came from *in vitro* experiments in which Hsp70 was added to preformed sHsp/substrate complexes. In the presence of ATP, Hsp70 was able to promote the folding of the protein to the native state (Figure 9).^[131] Independently, cell lysates were screened for factors that promote the refolding of sHsp-bound proteins.^[128, 134] These experiments also identified Hsp70 as the key player in the reactivation of proteins rescued from aggregation by sHsps.

The emerging picture is that sHsps function in binding non-native proteins once large quantities of unfolded proteins are formed, for example, as a consequence of stress conditions or overexpression of proteins. Binding prevents the formation of large aggregates and makes the subsequent refolding by Hsp70 or other potential ATP-dependent chaperone systems possible. This cooperation of different components of the cellular chaperone machinery thus allows two key properties of molecular chaperones, binding and folding, to be separated in space and time.

2.5. What Else Is out There?

The molecular chaperones introduced in Sections 2.1–2.4 constitute the major chaperone systems involved in protein folding. However, for the sake of clarity, we have omitted a

number of partner proteins that have been reported to interact with these chaperones. There are excellent review articles available that provide a more detailed picture for the dedicated readership.

As mentioned earlier, molecular chaperones are also important in other contexts in which protein conformations are manipulated. One of these processes is the resolubilization of protein aggregates. In the past years, some members of the Hsp100/Clp class of chaperones, namely ClpB from *E. coli* and Hsp104 from yeast, have been reported to dissolve protein aggregates. Importantly, these two chaperones require assistance from the Hsp70 system for their task.^[135, 136] Hsp100/Clp chaperones are also involved in protein degradation, during which they act as “unfoldases” and use the energy provided by ATP hydrolysis to actively unfold a target protein.^[137] Interestingly, all Hsp100/Clp chaperones form rings of six or seven subunits.

In the bacterium *E. coli*, many proteins designated for export associate with the chaperone SecB after their ribosomal synthesis.^[138–140] SecB was shown to arrest the folding of its client proteins. Subsequently, SecB guides its substrate to the translocation machinery, which transports it through the cytoplasmic membrane. Transport systems for unfolded proteins have also been found in some organelles of the eukaryotic cell, for example, in the mitochondria and in the endoplasmic reticulum.

3. Perspectives

The life cycle of a protein is marked by the conformational changes it has to undergo. Folding, trafficking, maintenance, and degradation of proteins are all processes that depend on the assistance of molecular chaperones. The past decade has witnessed an enormous increase in our understanding of these processes, and a large amount of both structural and functional data on chaperone proteins is now available. Despite these efforts, our knowledge and the picture that emerges remains sketchy. The variety of different chaperones is perplexing and at present we know only a little about their cellular function and how they accomplish their task(s) on a molecular level. There are several exciting directions in which this field is developing.

3.1. Chaperone Networks

An important question that remains to be answered is how the different classes of molecular chaperones cooperate in the cell. Examples of such chaperone networks are the cooperation between the Hsp90 system and the Hsp70 system during the activation of steroid hormone receptors (see Figure 7), or the cooperation between the Hsp70 and GroE in protein folding (Section 2.2.3). It is not clear whether the passage of a polypeptide substrate through such networks is vectorial or random.^[80, 141, 142] Another puzzling feature is the overlap in the function of the various chaperone classes. All chaperones are able to suppress the aggregation of folding proteins and are overproduced simultaneously under stress conditions.

While cells may require some functional overlap for backup purposes, much remains to be learned about the specific roles of individual classes of chaperones.

3.2. Conformational Changes of Proteins in Chaperone Complexes

In general, chaperone-mediated structural changes of polypeptides could involve folding, unfolding, and disassembly. Protein unfolding is a nonspecific process, as demonstrated by the fact that all known proteins can be unfolded by a single chemical compound, guanidine hydrochloride. Under cellular conditions, unfolding is an endergonic reaction and requires a source of energy. The function of a molecular chaperone would thus be to couple protein unfolding with the chemical energy provided by ATP hydrolysis so that the whole process becomes exergonic. Such an unfolding activity seems to be required for both protein degradation and for the recycling of misfolded proteins. A similar principle can be envisioned for the chaperone-assisted disassembly of defined protein complexes and of nonspecific aggregates. In both cases, the multiple interactions that stabilize the association of the components must be broken, which again requires the input of energy.

3.3. Chaperones and Disease

The importance of molecular chaperones for cell viability is illustrated by the fact that deletions of their genes are often lethal or cause severe cellular defects, such as reduced resistance to stress. If a specific chaperone activity is missing or reduced to subnormal levels, a disease may be the consequence. In other cases, the action of chaperones may cause a disease, as in the case of bovine spongiform encephalopathy or Creutzfeld–Jakob syndrome, which are both characterized by the deposition of fibrillous aggregates of the prion protein (PrP) in the brain.^[143] For mammalian prion diseases, the involvement of chaperones is still speculative. In yeast, however, prion formation was shown to be critically dependent on Hsp104.^[144] Hsp104 seems to regulate the size and the number of seeds that are required for fiber polymerization and propagation. In this case, cells can be cured by the inactivation of Hsp104.^[144, 145] In addition, chaperones are emerging as molecular targets for therapy in cancer, tissue transplantation, and septic shock syndrome, among others. Depending on their respective contribution, inhibition or stimulation of chaperone activity may be required for intervention.

3.4. Molecular Chaperones in Biotechnology

The production of recombinant proteins in bacteria is often impaired by the formation of inclusion bodies, which are large aggregates that consist mainly of inactive forms of the overexpressed protein.^[146] In some cases, this problem could

be alleviated by the simultaneous overproduction of molecular chaperones.^[147–149] Molecular chaperones may thus become useful tools to optimize biotechnical processes and to establish fine-tuned “cell factories” for the production of recombinant proteins.

3.5. Chaperones and Evolution

As mentioned earlier, small proteins usually do not require the assistance of molecular chaperones for in vitro folding, whereas larger proteins often do. Apparently, large proteins must confer certain evolutionary advantages on the cell, despite the additional expenses required for their production. Among others, two considerations may be important in this context: 1) The conformation space that is accessible for small proteins may be limited, that is, some three-dimensional structures can only be formed by longer polypeptide chains. Since the structure and the function of a protein are intimately related, some biological functions may be unique to large proteins. 2) Large proteins often comprise multiple domains, which have specific functions such as oligomerization, substrate binding, etc. This setup allows the creation of proteins with novel properties by a simple rearrangement of existing building blocks.

Another reason why chaperones have proven useful during molecular evolution concerns the conformational stability of proteins. Enzymes require flexibility to exert their biological function, for example, for binding substrates or for responding to regulatory signals. Thus, the three-dimensional structure has been selected for *optimum* stability, and not for *maximum* stability. Typically, the free energy of folding is in the range of 20–80 kJ mol^{−1},^[150] a value that corresponds to a small number of molecular interactions such as ion pairs or hydrogen bonds. The disadvantage of this low stability is that some proteins start to unfold at elevated temperatures. Therefore, a means is required to inhibit irreversible aggregation under these circumstances. The intimate relationship between chaperones and evolution is exemplified in a recent analysis of the function of Hsp90 during development.^[151] According to this study, this chaperone is essential to maintain the function of mutated proteins. Under stress conditions, this task can no longer be performed, and the mutations gain effect, thus resulting in new phenotypes and traits.

In summary, the analysis of chaperone function has taken a number of unexpected turns concerning both the molecular mechanisms of these ATP-driven molecular machines and their involvement in fundamental cellular processes. In contrast to their endangered human counterparts, molecular chaperones seem to be about to enter center stage. Their importance for the basic mechanisms that determine life at the molecular level is just beginning to be unveiled.

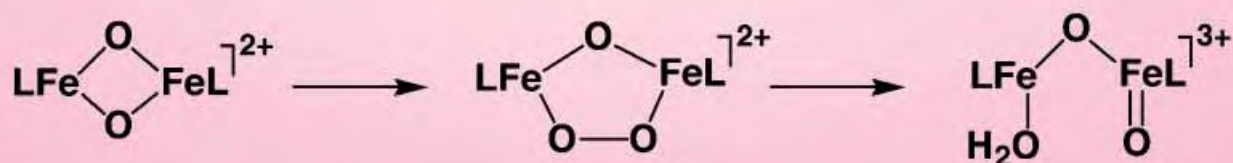
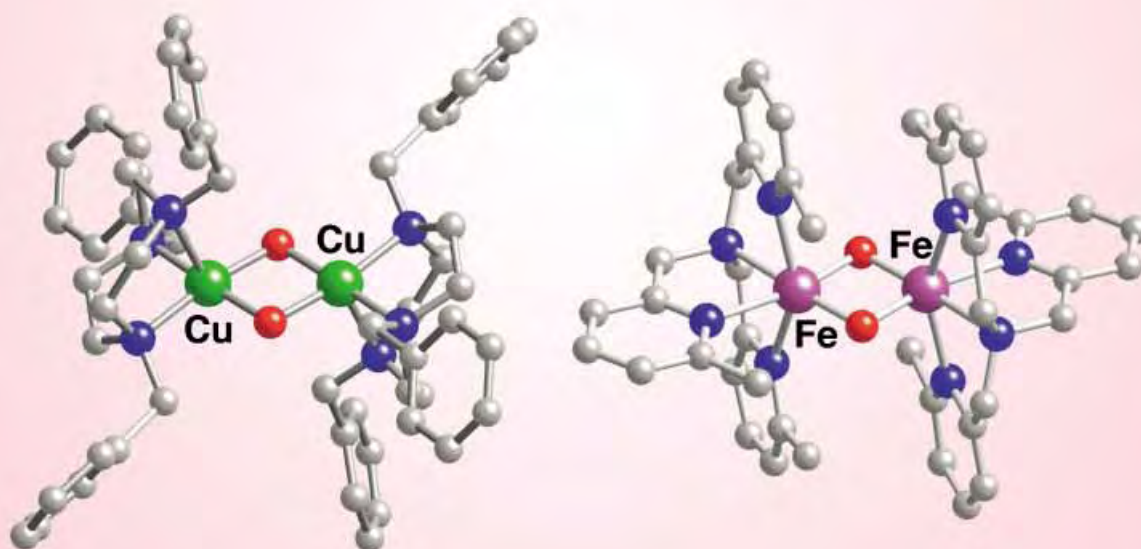
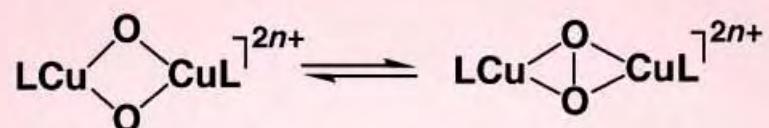
We thank Harald Wegele and Holger Grallert for reading the manuscript, and Rob Montfort for help with the preparation of Figure 8. Financial support by the DFG, the BMBF, the EU, and the FCI is gratefully acknowledged.

Received: August 1, 2001 [A 487]

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Copper and iron complexes containing the $M_2(\mu-O)_2$ core:
syntheses, structures, and reactivities



Bis(μ -oxo)dimetal “Diamond” Cores in Copper and Iron Complexes Relevant to Biocatalysis

Lawrence Que, Jr.* and William B. Tolman*

Although quite a familiar feature in high-valent manganese chemistry, the $M_2(\mu-O)_2$ diamond core motif has only recently been found in synthetic complexes for $M = Cu$ or Fe . Structural and spectroscopic characterization of these more reactive $Cu_2(\mu-O)_2$ and $Fe_2(\mu-O)_2$ compounds has been possible through use of appropriately designed supporting ligands, low-temperature handling methods, and techniques such as electrospray ionization mass spectrometry and X-ray crystallography with area detector instrumentation for rapid data collection. Despite differences in electronic structures that have been revealed through experimental and the-

oretical studies, $Cu_2(\mu-O)_2$ and $Fe_2(\mu-O)_2$ cores exhibit analogously covalent metal–oxo bonding, remarkably congruent Raman and extended X-ray absorption fine structure (EXAFS) signatures, and similar tendencies to abstract hydrogen atoms from substrates. Core isomerization is another common reaction attribute, although different pathways are traversed; for Fe , bridge-to-terminal oxo migration has been discovered, while for Cu , reversible formation of an O–O bond to yield a peroxo isomer has been identified. Our understanding of biocatalysis has been enhanced significantly through the isolation and com-

prehensive characterization of the $Cu_2(\mu-O)_2$ and $Fe_2(\mu-O)_2$ complexes. In particular, it has led to the development of new mechanistic notions about how non-heme multimetal enzymes, such as methane monooxygenases, fatty acid desaturase, and tyrosinase, may function in the activation of dioxygen to catalyze a diverse array of organic transformations.

Keywords: bioinorganic catalysis • copper • iron • metalloenzymes • metal–oxo complexes • oxygen activation

1. Introduction

Metal-promoted oxidations of organic compounds are of fundamental importance in organic synthesis, industrial catalysis, and enzymatic reactions. Chemists have long sought to unravel the mechanisms of such oxidations, with the ultimate objectives of inventing new reagents and exerting control over reactivity and selectivity. A key issue concerns the nature of the oxidizing species that is directly responsible for effecting the reaction. In some cases the oxidant is not metal-based (e.g. an organic radical derived from an autoxidation process), while in others a metal–oxygen species of some sort is implicated as the reactive intermediate.^[1] Thorough characterization of such metal–oxygen species is critical for obtaining detailed mechanistic insights, but by their very nature as reactive oxidizing molecules they are

difficult to isolate or even observe directly. The problem is exacerbated for oxidants comprising metal ions from the mid-to-late first-row transition series, such as iron and copper, that are particularly labile and active in many biochemically significant processes. These attributes are exemplified by heme–iron proteins and complexes, extensive studies of which have provided the mechanistic paradigm for dioxygen activation at a metal center.^[2]

Recent work has centered on non-heme iron and copper sites in biology, in particular those with two proximal metal ions that yield novel oxidizing intermediates capable of performing diverse organic functionalizations.^[3] Notable examples of these sites and corresponding structures for selected intermediates that have been postulated to be involved in their reactions are listed in Table 1.^[3, 4] Significant insights into these dimetal systems have been attained through the synthetic modeling approach,^[5] whereby the detailed characterization of O_2 adducts or derived species provides fundamental spectroscopic, structural, and reactivity benchmarks for understanding the metalloprotein sites and, ultimately, developing new catalysts.^[6] Of particular consequence in this regard is the recent discovery of a new class of iron and copper complexes that contain the simple “diamond-

[*] Prof. Dr. L. Que, Jr., Prof. Dr. W. B. Tolman
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota
207 Pleasant Street SE
Minneapolis, MN 55455 (USA)
Fax: (+1) 612-624-7029
E-mail: que@chem.umn.edu, tolman@chem.umn.edu

Table 1. Examples of enzymes with non-heme diiron or copper active sites and key intermediates involved in catalysis.

Enzymes	Reaction catalyzed	Intermediates observed and <i>postulated</i> [a]	Ref.
methane monooxygenase	$\text{CH}_4 + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{CH}_3\text{OH} + \text{H}_2\text{O}$	MMOH- P : (μ -peroxo)diiron(III,III) MMOH- Q : bis(μ -oxo)diiron(IV,IV)	[3a,b,h]
fatty acid desaturase	$\text{R}(\text{CH}_2)_m\text{CH}_2\text{--CH}_2(\text{CH}_2)_n\text{COOH} + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{R}(\text{CH}_2)_m\text{CH=CH}(\text{CH}_2)_n\text{COOH} + 2\text{H}_2\text{O}$	(μ -1,2-peroxo)diiron(III,III), bis(μ -oxo)diiron(IV,IV)	[4a]
ribonucleotide reductase (cofactor generation)	$\text{Fe}^{\text{II}}\text{Fe}^{\text{II}} + \text{Tyr 122-OH} + \text{O}_2 + \text{H}^+ + \text{e}^- \rightarrow \text{Fe}^{\text{III}}\text{-O-Fe}^{\text{III}} + \text{Tyr 122-O}^\bullet + \text{H}_2\text{O}$	RNR-R2- P : (μ -1,2-peroxo)diiron(III,III) RNR R2- X : (μ -oxo)iron(III)iron(IV)	[3a,c, 4b]
ferritin (ferroxidase activity)	$4\text{Fe}^{\text{II}} + \text{O}_2 + 4\text{H}^+ \rightarrow 4\text{Fe}^{\text{III}} + 2\text{H}_2\text{O}$	(μ -1,2-peroxo)diiron(III,III)	[4c,d]
tyrosinase	$\text{Tyrosine} + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{DOPA} + \text{H}_2\text{O} \rightarrow \text{dopaquinone} + 2\text{e}^-$	(μ - η^2 : η^2 -peroxo)dicopper(II,II), bis(μ -oxo)dicopper(III,III)	[3d,f,i, 99]

[a] See Scheme 3 for illustrations.

shaped" $[\text{M}_2(\mu\text{-O})_2]^{n+}$ core structure (Figure 1, $\text{M} = \text{Fe}$ or Cu). While this bis(μ -oxo)dimetal motif is known for many complexes of metal ions from the early half of the first-row transition metal series (e.g. $\text{M} = \text{Ti}$,^[7] V ,^[8] Cr ,^[9] Mn ^[10]) for which the complexes are usually quite stable, it had only been a figment of chemists' imaginations for complexes of the latter-half ions $\text{M} = \text{Fe}$, Co , Ni , or Cu until the recent

successful synthetic work. New notions about how non-heme, multimetal enzymes function have arisen as a result of studies of these compounds.

In this Review we take a specific view towards uncovering general underlying chemical principles and drawing comparisons among the synthetic bis(μ -oxo)dimetal systems comprising iron and copper centers, with mention of species with

William B. Tolman (right) was born on May 20, 1961, in Cleveland, Ohio. As an undergraduate at Wesleyan University, Middletown, Connecticut (B.A. in 1983), he worked in the laboratory of Prof. Alan Cutler doing organometallic chemistry research. He obtained a Ph.D. in chemistry from the University of California, Berkeley, in 1987, under the advisorship of Prof. K. Peter C. Vollhardt. His interests shifted toward bioinorganic chemistry during a stint in the laboratory of Prof. Stephen J. Lippard at the Massachusetts Institute of Technology, where he was a National Institutes of Health and American Cancer Society Postdoctoral Fellow. He joined the faculty at the University of Minnesota in 1990 and currently is a Distinguished McKnight University Professor. He has received the Buck–Whitney Medal (American Chemical Society), a National Young Investigator Award (National Science Foundation), a Searle Scholar Award, a Camille and Henry Dreyfus Teacher-Scholar Award, and an Alfred P. Sloan Foundation Research Fellowship. Current research in his laboratory is focused on synthetic modeling of metalloprotein active sites and developing new catalysts for biodegradable polymer synthesis. Most of the rest of his time is spent happily with his wife, Bonnie, and three children, Sarah, Claire, and Simon.



L. Que, Jr.

W. B. Tolman

Lawrence Que, Jr. (left) was born on April 23, 1949 in Manila, the Philippines, and obtained his Bachelor's degree in Chemistry from Ateneo de Manila University in 1969. He then pursued graduate studies in coordination chemistry at the University of Minnesota under Prof. Louis H. Pignolet (Ph.D. 1973). After postdoctoral stints in bioinorganic chemistry with Prof. Richard H. Holm at the Massachusetts Institute of Technology and Professor Eckard Münck at the University of Minnesota, he joined the Cornell University faculty in 1977. In 1983 he returned to the University of Minnesota, where he is now 3M/Alumni Distinguished Professor of Chemistry and Co-Director of the Center for Metals in Biocatalysis. In addition, he is currently serving as the Chief Editor for the Journal of Biological Inorganic Chemistry. Among his awards are an Alfred P. Sloan Foundation Research Fellowship and Research Career Development and MERIT Awards from the National Institutes of Health. His research interests have focused principally on unraveling the mechanisms of dioxygen activation by non-heme iron enzymes using both biophysical and biomimetic approaches, which allows his group to explore the spectroscopic and mechanistic properties of metalloenzymes as well as the design and synthesis of structural and functional models of these enzymes. A key aspect of the work in the past few years is the development of strategies for trapping and characterisation of important reaction intermediates, such as those discussed in this review. The biomimetic studies have also led to a new research direction in asymmetric and 'green' oxidation catalysis. His interests outside of science include enjoying the outdoors and supporting the performing arts, together with wife Deb and daughters Emily and Erin.

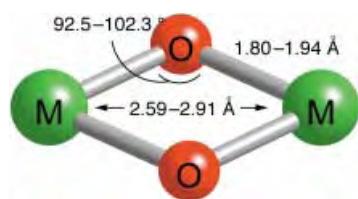


Figure 1. Range of selected interatomic distances and angles in bis(μ -oxo)-dimetal cores (see Table 3).

cobalt and nickel as well. These aims will be addressed through discussion of the extensive efforts to characterize the complexes by experimental and theoretical methods and to understand their reactivity. We then consider the relevance of these results to dioxygen activation processes in biological catalysis. Aspects of the chemistry presented here have been reviewed.^[11–13]

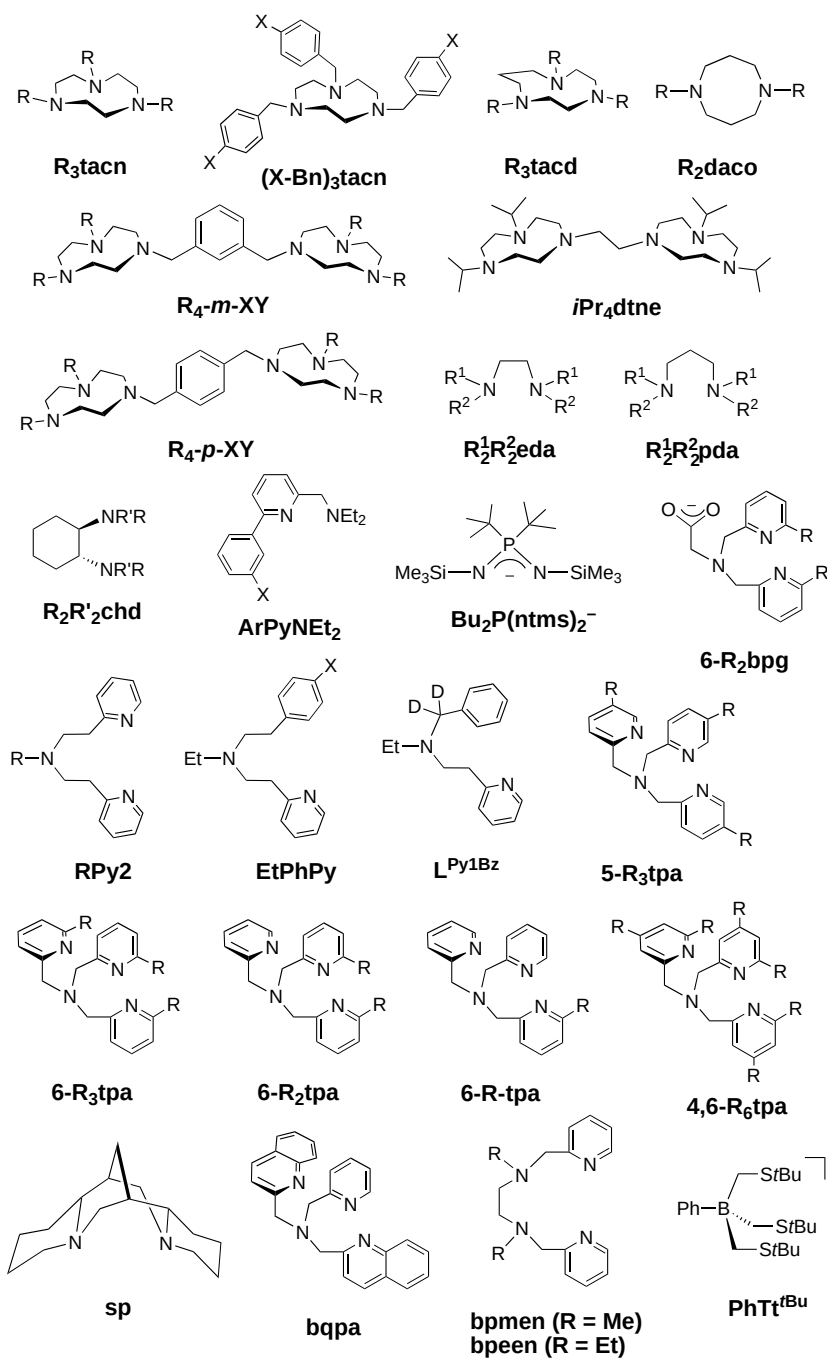
2. Synthetic Considerations

2.1. General Comments

As mentioned above, complexes with the $[M_2(\mu-O)_2]^{n+}$ core have been known for many years for $M = Mn$ with oxidation states (III,III), (III,IV), and (IV,IV).^[10] These $[Mn_2(\mu-O)_2]^{n+}$ compounds are thermodynamically quite stable, and they typically are isolated as crystalline solids that endure for long periods under ambient conditions. The situation for the latter half of the first row transition metal ions $M = Fe$, Co ,^[14] Ni ,^[14–17] or Cu is rather different, insofar as these bis(μ -oxo)dimetal cores tend to be rather reactive and unstable at room temperature. The successful isolation and characterization of complexes of these metals was made possible by the use of two key synthetic strategies: a) low-temperature handling of solutions and solids to slow undesired decomposition reactions, and b) use of chelating supporting ligands, usually with alkyl substituents, that facilitate crystallization and inhibit intermolecular interactions (Scheme 1). These methods have precedents, in particular for the isolation of heme-iron and copper complexes with oxo, superoxo, or peroxo groups.^[2, 6c, 18] Technological advances also have been critical for the recent successful characterization of the $[M_2(\mu-O)_2]^{n+}$ ($M = Fe$, Co , Ni , Cu) compounds; the availability of electrospray ionization mass spectrometry (ESI-MS)^[19] and area detector X-ray diffraction instrumentation for rapid data collection on temperature-sensitive solutions and crys-

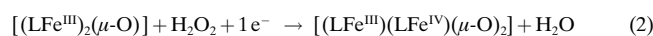
tals, respectively, has been of particular value. Finally, the development of reproducible preparations of suitably designed precursor molecules is a key prerequisite in most synthetic endeavors, and extensive efforts toward this end were necessary to obtain the target bis(μ -oxo) complexes in sufficient purity and quantity for thorough characterization.

The methods used in attempts to prepare the bis(μ -oxo)diiron and -dicopper compounds have involved reactions of the generalized type shown in Equations (1)–(3) (not all balanced). In the reaction in Equation (1) four-electron reduction of O_2 is accomplished by a Cu^I precursor, which

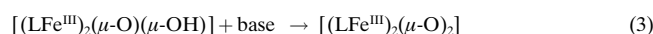


Scheme 1. Ligands used to prepare complexes with $[M_2(\mu-O)_2]^{n+}$ cores, with abbreviations that are used in the text.

results in incorporation of both O atoms into the bis(μ -oxo)dicopper core. This method has been the major one used for the isolation of the copper compounds, although it has been examined in a few instances in attempts to prepare iron congeners and in one case for nickel.^[17] The route in Equation (2) involves the reduction of H_2O_2 by a diiron(III)



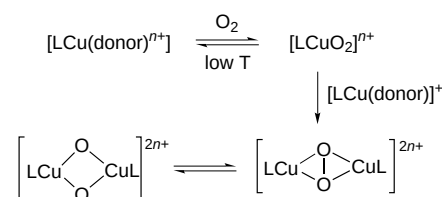
precursor, and resembles the so-called “shunt” pathway used in heme iron enzymes and complexes for the generation of monoiron-oxo intermediates.^[2] A similar method has been used to convert bis(μ -hydroxo)dinickel(II,II) and -dicobalt(II,II) complexes into their respective bis(μ -oxo)dimetal(III,III) relatives.^[14–16] Equation (3) depicts another route involving deprotonation of a bridging hydroxide ligand in a diiron(III,III) precursor. Specific details of the preparations used for the Cu and Fe cases are summarized in the following section.



2.2. Specific Syntheses

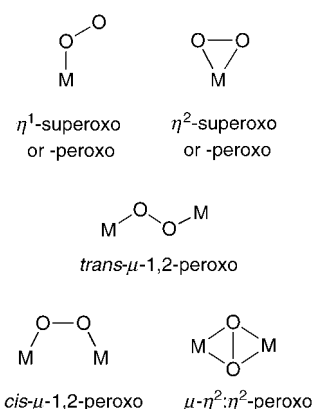
2.2.1. Bis(μ -oxo)dicopper(III,III)

Treatment of LCu^{I} complexes with O_2 (1 atm) at low temperatures ($< -40^\circ\text{C}$) is the usual method for the synthesis of the bis(μ -oxo)dicopper compounds, which have been prepared using a wide range of ligands (Schemes 1 and 2).^[20–37] Product identification was accomplished through



Scheme 2. Generalized course of the formation of bis(μ -oxo)dicopper complexes through the oxygenation of copper(I) precursors with supporting ligands L (Scheme 1). Donor = CH_3CN or $\text{CH}_2=\text{CH}_2$. Charges (n) are 1 for $\text{L} = \text{R}_3\text{tacn}$ ($\text{R} = \text{Me}$, $i\text{Pr}$, aryl ether dendrimer), $(\text{X-Bn})_3\text{tacn}$, $\frac{1}{2}i\text{Pr}_4\text{dtne}$, $\frac{1}{2}i\text{Pr}_4\text{-}p\text{-XY}$, R_2daco , $\text{R}_2\text{R}'_2\text{chd}$ (R , $\text{R}' = \text{Me}$, Et), $\text{R}'_2\text{R}_2\text{pda}$, $\text{R}'_2\text{R}'_2\text{eda}$, MePy_2 , EtPhPy , $6\text{-R}_2\text{tpa}$, and ArPyNEt_2 ; $n = 0$, $\text{L} = \text{Bu}_2\text{P}(\text{ntms})_2^-$.

spectroscopic studies and, in selected instances, by X-ray crystallography and low-temperature ESI-MS. Mechanistic data for the oxygenation reaction are available in several instances from variable-temperature stopped-flow kinetics experiments.^[21, 23, 24, 27] The data support the pathway shown in Scheme 2 involving initial formation of a 1:1 $\text{Cu}:\text{O}_2$ adduct, presumably a (superoxo)copper(II) species akin to previously identified examples (Scheme 3).^[18, 38] This step is followed by trapping by a second Cu^{I} species to yield a (μ -peroxo)dicopper(II,II) intermediate that subsequently undergoes O–O bond breaking to afford the final bis(μ -oxo)dicopper(III,III) product. Product solutions and/or solids comprising only peroxo, only bis(μ -oxo), or mixtures of both have been identified, with the implication that the nature of the supporting ligand L is critical for determining whether or not the O–O bond breaks.



Scheme 3. Nomenclature for common metal–dioxygen adduct structures.

Direct evidence in support of the equilibrium in Scheme 2 between peroxo- and bis(μ -oxo)dicopper complexes is available in a few instances,^[21, 33, 35, 39] but in others the evidence is indirect or not available. These issues are further discussed below in Section 6.1.

Although the overall pathway drawn in Scheme 2 appears to be general, differences in the relative rates of the individual steps have been observed. For the series of macrocyclic ligands $\text{L} = \text{R}_2\text{R}'_2\text{tacn}$ ($\text{R} = \text{R}' = i\text{Pr}$; $\text{R} = i\text{Pr}$, $\text{R}' = \text{Bn}$; $\text{tacn} = 1,4,7\text{-triazacyclononane}$), $i\text{Pr}_4\text{-}m\text{-XY}$, and $i\text{Pr}_4\text{-}p\text{-XY}$, and $\frac{1}{2}i\text{Pr}_4\text{dtne}$ ($\text{dtne} = 1,2\text{-di}(1,4,7\text{-triazacyclononyl})\text{ethane}$), the kinetic data show that 1:1 $\text{Cu}:\text{O}_2$ adduct formation is rate-determining, so that the rate of product (P) formation is described by the expression: $d[\text{P}]/dt = k[\text{O}_2][\text{Cu}^{\text{I}} \text{ complex}]$. Selected activation parameters for this step are listed in Table 2. Mixtures of peroxo and bis(μ -oxo) species that must

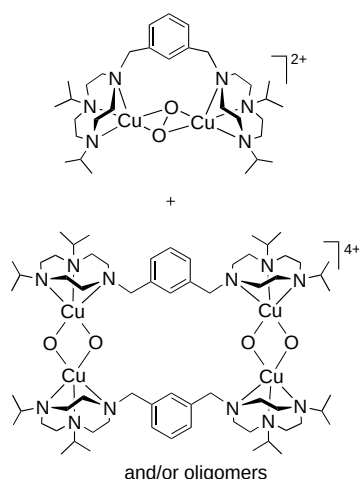
Table 2. Selected activation parameters for oxygenations of Cu^{I} complexes.

Supporting ligand	$\Delta H^\ddagger$ [kJ mol ^{−1}]	$\Delta S^\ddagger$ [J mol ^{−1} K ^{−1}]	Rate law ^[a]	Ref.
$i\text{Pr}_3\text{tacn}$	37.2(5)	−62(2)	$k[\text{O}_2][\text{complex}]$	[21]
$i\text{Pr}_4\text{-}m\text{-XY}$	39.4(5)	−30(2)	$k[\text{O}_2][\text{complex}]$	[24]
$i\text{Pr}_4\text{dtne}$	39.4(1)	−32.0(4)	$k[\text{O}_2][\text{complex}]$	[23]

[a] Rate law for the formation of bis(μ -oxo)- and/or peroxodicopper products.

rapidly equilibrate to explain the observed kinetics are seen for $\text{L} = i\text{Pr}_3\text{tacn}$, but sole bis(μ -oxo) complex generation occurs for $\text{L} = \text{Bn}_3\text{tacn}$, $\frac{1}{2}i\text{Pr}_4\text{dtne}$, and $i\text{Pr}_4\text{-}p\text{-XY}$ (as well as for other ligands for which oxygenation kinetics data are not available). For $i\text{Pr}_4\text{-}m\text{-XY}$ the situation is more complicated because of competition between intramolecular peroxo and intermolecular bis(μ -oxo) complex formation after the initial O_2 binding step (Scheme 4).

Different kinetic behavior is observed for $\text{L} = \text{EtPhPy}$ or RPy_2 ($\text{R} = \text{PhCH}_2\text{CH}_2$; for structures see Scheme 1), where the rates of product formation have second-order dependencies on $[\text{LCu}^{\text{I}}]$.^[27, 40] These findings suggest that the trapping of LCuO_2 by LCu^{I} is rate-controlling in these instances. Note that the observable product for the RPy_2 case is the (μ - $\eta^2:\eta^2$ -peroxo)dicopper complex and that a derived bis(μ -oxo)

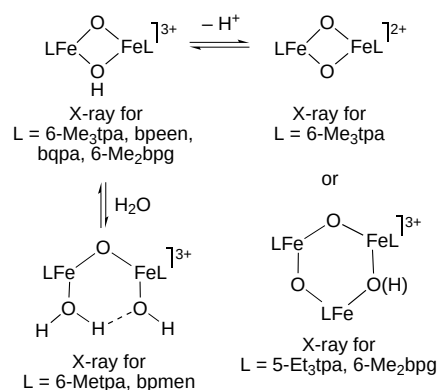


Scheme 4. The two products observed upon oxygenation of the dicopper(II) complex of *i*Pr₄-*m*-XY, with the “intramolecular” adduct (top) favored in dilute solution (<0.1 mM) and the “intermolecular” species (bottom) predominant at high concentrations (>2.0 mM).^[24]

species is only implicated from decomposition kinetics results. At this juncture, it is not clear what controls the relative rates of 1:1 adduct formation and subsequent trapping by Cu^I in the complexes that yield bis(μ -oxo) products, but these issues have been addressed for alternate copper-containing systems that form other types of oxygenated intermediates.^[41]

2.2.2. Bis(μ -oxo)diiron(III,III)

The synthesis of the first crystallographically characterized bis(μ -oxo)diiron complex, a diiron(III,III) species,^[42] was based on the facile acid/base/aquation chemistry outlined in Scheme 5.^[43] The relative stabilities of the various species shown differ with the capping ligand L, and examples of each type have been structurally characterized. The complexes



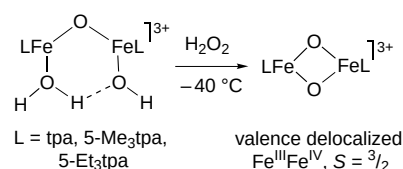
Scheme 5. Interconversions observed for various aqua, hydroxo, and oxo-iron species. Those that have been characterized by X-ray crystallography are so noted.^[43, 47]

$[L_2Fe_2(\mu-O)(\mu-OH)]^{3+}$ are noteworthy because of the novelty of their core structure (previously seen only for $M = Mn^{IV}$ ^[44] and Cr^{III} ^[45]) and their utility for drawing comparisons to bis(μ -oxo) species. They were prepared by oxidation of Fe^{II} salts by *t*BuOOH in the presence of L^[43, 46] or by reaction of

$[L_2Fe_2(\mu-O)(OAc)]^+$ with Et₃N in MeOH (L = 6-Me₂bpg; see Scheme 1).^[47] These compounds serve as useful precursors of oxo-bridged polyiron(III) compounds by deprotonation reactions (pK_a values $\approx 16-18$ in CH₃CN). In particular, for L = 6-Me₃tpa or 4,6-Me₆tpa, (for structures see Scheme 1) treatment of $[L_2Fe_2(\mu-O)(\mu-OH)]^{3+}$ (pK_a 15.9 and 16.3, respectively, in CH₃CN) with Et₃N yielded $[L_2Fe_2(\mu-O)_2]^{2+}$. With other ligands that lack the 6-Me substituents, trinuclear complexes form instead, $[L_3Fe_3(\mu_2-O)_3]^{3+}$ (L = 5-Et₃tpa) or $[L_3Fe_3(\mu_2-O)_2(\mu-OH)]^+$ (L = 6-Me₂bpg; Scheme 5).^[43, 47]

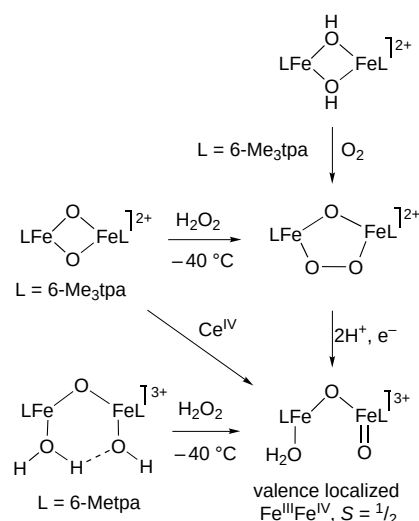
2.2.3. Bis(μ -oxo)diiron(III,IV) and Related Species

Reaction of $[L_2Fe_2(\mu-O)(OH)(H_2O)]^{3+}$ (Scheme 6; L = tpa, 5-Me₃tpa, or 5-Et₃tpa) with H₂O₂ at $T = -40^\circ C$ leads to the generation of a deep green species.^[48] On the basis of extensive data from spectroscopic, ESI-MS,^[48] and X-ray crystallographic (L = 5-Et₃tpa) studies,^[49] this species was identified as $[L_2Fe_2(\mu-O)_2]^{3+}$. As described in greater detail below, it is best described as a valence-delocalized molecule comprising a magnetically coupled low-spin ($S = 1/2$) Fe^{III}/low-spin ($S = 1$) Fe^{IV} pair that yields an overall $S = 3/2$ ground state.



Scheme 6. Synthesis of $[L_2Fe_2(\mu-O)_2]^{3+}$, where L = tpa, 5-Me₃tpa, or 5-Et₃tpa.^[48b, 49]

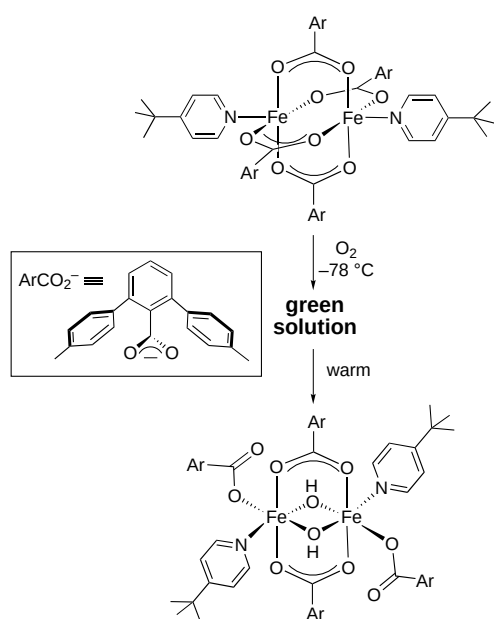
A related diiron(III,IV) complex with L = 6-Metpa was accessed in a similar way, but the relatively small difference in the ligand substituent pattern (6-H $\rightarrow$ 6-Me on one pendant pyridine) resulted in important electronic structural and, apparently, geometric changes (Scheme 7).^[50] While the product formulation for L = 6-Metpa is $[L_2Fe_2(O)_2]^{3+}$, EPR



Scheme 7. Formation of diiron(III,IV) complexes supported by 6-Metpa or 6-Me₃tpa ligands.^[50, 52, 53]

and Mössbauer spectroscopic results indicate that it contains a valence localized, antiferromagnetically coupled high-spin Fe^{III} /high-spin Fe^{IV} pair with an $S = \frac{1}{2}$ ground state. Its spectral features resemble those of a key biological intermediate, compound "X" in ribonucleotide reductase (see Section 7).^[3a,c] A species with similar properties results from treatment of $[\text{L}_2\text{Fe}_2(\mu\text{-O})_2]^{2+}$ ($\text{L} = 6\text{-Me}_3\text{tpa}$) with H_2O_2 .^[51] In this instance, the high-valent species formed via an intermediate with a $(\mu\text{-peroxo})(\mu\text{-oxo})$ diiron(III,III) core (Scheme 7). Oxygenation of a bis(μ -hydroxo)diiron(II,II) precursor capped by 6- Me_3tpa led to the same peroxo intermediate and high valent product.^[52] In more recent work, this $S = \frac{1}{2}$ product also was generated from chemical or electrochemical oxidation of $[\text{L}_2\text{Fe}_2(\mu\text{-O})_2]^{2+}$ ($\text{L} = 6\text{-Me}_3\text{tpa}$) and the accumulated evidence indicated that it has one bridging and one terminal oxo unit derived from ring-opening isomerization of the bis(μ -oxo)diiron(III,IV) core.^[53]

An $S = \frac{1}{2}$ $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ complex is also accessible with quite different supporting donors from those supplied by the tpa frame. Treatment of a CH_2Cl_2 solution of the paddlewheel complexes $[\text{Fe}_2(\text{O}_2\text{CAR})_4(4\text{-}t\text{BuPy})_2]$ with O_2 at -78°C led to the formation of a metastable green solution which decomposed upon warming to yield a bis(μ -hydroxo)bis(μ -1,3-carboxylato)diiron(III,III) compound (Scheme 8).^[54] On the basis of EPR and Mössbauer spectroscopic data, it was suggested that the green solution contained a mixture of three species: 1) an antiferromagnetically coupled diiron(II,III) complex, 2) an $S = \frac{1}{2}$ $\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}$ compound that is the green chromophore,^[55] and 3) an $S = \frac{1}{2}$ $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ complex. The latter species was postulated to contain a bis(μ -oxo) motif on the basis of the literature evidence available at the time, but the recent identification of the isomeric bridging/terminal oxo arrangement for at least one of the $S = \frac{1}{2}$ species ($\text{L} = 6\text{-Me}_3\text{tpa}$, derived from chemical oxidation)^[53] suggests that this alternate structure should be considered.



Scheme 8. Oxygenation of a diiron(II,II) complex supported by a sterically hindered carboxylate ligand.^[54, 55]

3. X-ray Structures

Characterization of the bis(μ -oxo)dicopper and -diiron complexes by X-ray crystallography has been critical for conclusively identifying their novel cores, enabling detailed analysis of spectroscopic and physicochemical data, and providing a solid foundation for the drawing of comparisons to data acquired on relevant metalloproteins. The thermal instability of the complexes rendered such characterization difficult, but application of low-temperature handling techniques and rapid data-collection methods by using area detector instrumentation resulted in a number of successful structure determinations. Selected interatomic distances and angles for all complexes with $[\text{M}_2(\mu\text{-O})_2]^{n+}$ ($\text{M} = \text{Cu}$ or Fe) cores reported to date are listed in Table 3. For comparative purposes, data for selected compounds with Ni^{II} ^[14, 15, 17] and Co^{II} ^[14] cores and those with related core structures (e.g., hydroxo-bridged) also are listed.

A survey of the parameters shown in Table 3 reveals a general similarity among a wide variety of complexes with the bis(μ -oxo)dimetal motif; this is summarized in the schematic representation in Figure 1. In spite of differences in the metal ions, their oxidation level, and the supporting ligands, a relatively narrow range of distances and angles is observed for the $[\text{M}_2(\mu\text{-O})_2]^{n+}$ unit. This lack of variation in structural parameters with differences in metal oxidation state and ligands was previously noted for $\text{M} = \text{Mn}$,^[10] but must now be extended to include disparate metal ions with differing coordination numbers as well. As shown in Figure 1, the important general characteristics of the core that in combination distinguish it from related structures are the short intermetal and metal-oxo distances, essentially planar M_2O_2 arrangement, and acute M-O-M angles. Replacement of a μ -oxo bridge(s) with a μ -hydroxo unit(s) usually results in core expansion as reflected in lengthened $\text{M}\cdots\text{M}$ and $\text{M}-\text{O}$ distances and larger M-O-M angles, although the presence of additional bridging ligands such as carboxylates can counteract this effect.^[56, 57] Specific comparisons are described in greater detail below.

3.1. Copper

Representations of the X-ray structures reported to date of bis(μ -oxo)dicopper complexes are shown in Figure 2. While they have analogous $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ core metrical parameters (Table 3, entries 1–4 and 6), differences in metal coordination numbers and geometries correlate with the number of N-donors in the different supporting ligands. Thus, each copper ion is four-coordinate square planar with the bidentate $\text{Me}_2\text{Et}_2\text{chd}$ ^[26] or $\text{Bu}_2\text{P}(\text{ntms})_2$ ^[32] (for structures see Scheme 1) ligands, five-coordinate square pyramidal with the facially coordinating tridentate Bn_3tacn and $i\text{Pr}_4\text{dtne}$,^[21–23] ligands and six-coordinate distorted octahedral with the tetradentate tripodal 6- Me_3tpa ligand.^[30] The neutral complex supported by the $\text{Bu}_2\text{P}(\text{ntms})_2$ ^[32] ligand is somewhat anomalous with respect to its core geometry, as it exhibits rather long $\text{Cu}\cdots\text{Cu}$ and $\text{Cu}-\text{O}$ distances (Table 3, entry 6). As would be expected for copper in the +III or +II oxida-

Table 3. Structural data for bis(μ -oxo)dimetal and related complexes.^[a]

Entry	Core	Supporting ligands ^[b]	M...M	M–O	$\angle$ M–O–M	Ref.
1	$\text{Cu}_2^{\text{III}}(\mu\text{-O})_2$	$\text{Me}_2\text{Et}_2\text{chd}$	2.743(1)	1.814(6) 1.809(6) 1.796(6) 1.804(6)	98.9(3) 98.8(3)	[26]
2		$\text{Bn}_3\text{tacn}^{[c]}$	2.794(2)	1.803(5) 1.808(5)	101.4(2)	[21, 22]
3		$i\text{Pr}_4\text{dtne}^{[c]}$	2.793(1)	1.827(4) 1.836(4) 1.824(4) 1.823(4)	99.3(2) 99.0(2)	[23]
4		6- Me_2tpa	2.758(4)	1.806(9) 1.799(8)	99.8(4)	[30]
5		$\text{MePy}_2^{[d]}$	3.445(2)	1.905(5) 1.922(6)	128.4(3)	[28]
6		$\text{Bu}_2\text{P}(\text{ntms})_2^-$	2.906(1)	1.865 (3) 1.864(3)	102.3(2)	[32]
7		$\text{Et}_4\text{eda}^{[e]}$	2.75	1.80		[77a]
8		$\text{Me}_4\text{pda}^{[e]}$	2.85	1.81		[34]
9	$\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}(\mu\text{-O})_2$	5- Et_3tpa	2.683(1)	1.805(3) 1.860(3)	94.07(1)	[49]
10		5- $\text{Me}_3\text{tpa}^{[e]}$	2.59	1.77 1.94		[48b]
11	$\text{Fe}_2^{\text{III}}(\mu\text{-O})_2$	6- Me_3tpa	2.716(2)	1.844(3) 1.916(4)	92.5(2)	[42, 43]
12	$\text{Fe}_2^{\text{III}}(\mu\text{-O})(\mu\text{-OH})$	bpeen	2.835(1)	1.850(3) 1.976(4) 1.846(3) 1.993(4)	91.1(2) 100.2(2)	[42]
13		Me_2bpg	2.899(2)	1.873(8) 1.962(6)	91.5(3) 103.9(4)	[47]
14	$\text{Fe}_2^{\text{III}}(\mu\text{-OH})_2$	4- $\text{Me}_2\text{Ndipic}^{[f]}$	3.118(3)	1.937(6) 1.986(9)	105.3(4)	[61b]
15		ArCO_2^- , $\text{Bn}_2\text{en}/\text{Bnen}^{[g]}$	2.9788(6)	1.9726(17) 1.9977(17) 1.9852(17) 1.9805(16)	96.97(7) 97.64(7)	[56]
16		ArCO_2^- , pyridine ^[h]	2.8843(9)	2.012(2) 1.986(2)	92.33(10)	[57]
17	$\text{Ni}_2^{\text{III}}(\mu\text{-O})_2$	$\text{Tp}^{\text{Me}_2}^{[i]}$	2.882(3)	1.841(7) 1.870(8)	101.9(3)	[14]
18		6- Me_3tpa	2.924(1)	1.888(6) 1.854(7)	102.8(3)	[15]
19		$\text{PhTt}^{(\text{Bu})[c]}$	2.83	1.82		[17]
20	$\text{Co}_2^{\text{III}}(\mu\text{-O})_2$	$\text{Tp}^{\text{Me}_2}^{[i]}$	2.728(2)	1.783(4) 1.796(5)	99.3(2)	[14]
21	$\text{Ga}_2^{\text{III}}(\mu\text{-O})_2$	$\text{L}^{\text{dipp}}^{[j]}$	2.5989(3)	1.8536(9) 1.8485(9)	88.18(4)	[64]

[a] Except where indicated, data are from X-ray crystal structures, distances [Å], angles [°], and estimated standard deviations indicated in parentheses. [b] Except where indicated, ligand abbreviations correspond to structures shown in Scheme 1. [c] Ligands with perdeuterated substituents were used. [d] Structural data (e.g. $\text{O}\cdots\text{O} = 1.666(12)$ Å) indicates compositional disorder (solid solution) of bis(μ -oxo)- and μ - η^2 : η^2 -peroxodicopper isomers. [e] Data are from EXAFS results. [f] 4-dimethylamino-2,6-dicarboxylatopyridine. [g] $\text{ArCO}_2^- = 2,6$ -ditolylbenzoate, with $[\text{Fe}_2(\mu\text{-OH})_2(1,2\text{-}\mu\text{-ArCO}_2)_2]^{2+}$ core. [h] $\text{ArCO}_2^- = 2,6$ -ditolylbenzoate, $\text{Bn}_2\text{en} = N,N$ -dibenzylethylenediamine, $\text{Bnen} = N$ -benzylethylenediamine, with $[\text{Fe}_2(\mu\text{-OH})_2(1,2\text{-}\mu\text{-ArCO}_2)_2]^{3+}$ core. [i] $\text{Tp}^{\text{Me}_2} = \text{tris}(3,5\text{-dimethylpyrazolyl})\text{hydroborate}$. [j] $\text{L}^{\text{dipp}} = 2,4\text{-bis}(2,6\text{-diisopropylphenylimido})\text{pentane}$.

tion levels, distances between the metal ion and the axial donors in the square-pyramidal and distorted octahedral-geometries are elongated relative to the equatorial metal–ligand separations (data not listed). The axial donors adopt an *anti* arrangement in the Bn_3tacn -supported case, but they are *syn* in the complex with $i\text{Pr}_4\text{dtne}$ as a result of the constraints of the ethylene tether between the macrocycles in this ligand. The $i\text{Pr}_4\text{dtne}$ tether also appears to induce a slight distortion of the bis(μ -oxo) core from planarity, as indicated by the dihedral angle between the O–Cu–O and Cu–O–Cu planes of $\sim 13^\circ$.^[23]

It is useful to compare the structural features common to the $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ cores to those of related $[\text{Cu}_2(\mu\text{-OH})_2]^{2+}$ and $[\text{Cu}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)]^{2+}$ units supported by similar ligands (Figure 3).^[22, 58] As noted above, the intermetal and metal–oxygen distances are increased in the $[\text{Cu}_2(\mu\text{-OH})_2]^{2+}$ core. However, caution should be exercised in differentiating bis(oxo)- from bis(hydroxo)dicopper cores on the basis of intermetal separations alone, since a long Cu...Cu separation of 2.906(1) Å was seen in the neutral bis(μ -oxo)dicopper complex supported by $\text{Bu}_2\text{P}(\text{ntms})_2^-$ ions.^[32] The Cu...Cu separation in the (μ - η^2 : η^2 -peroxo)dicopper isomer of the

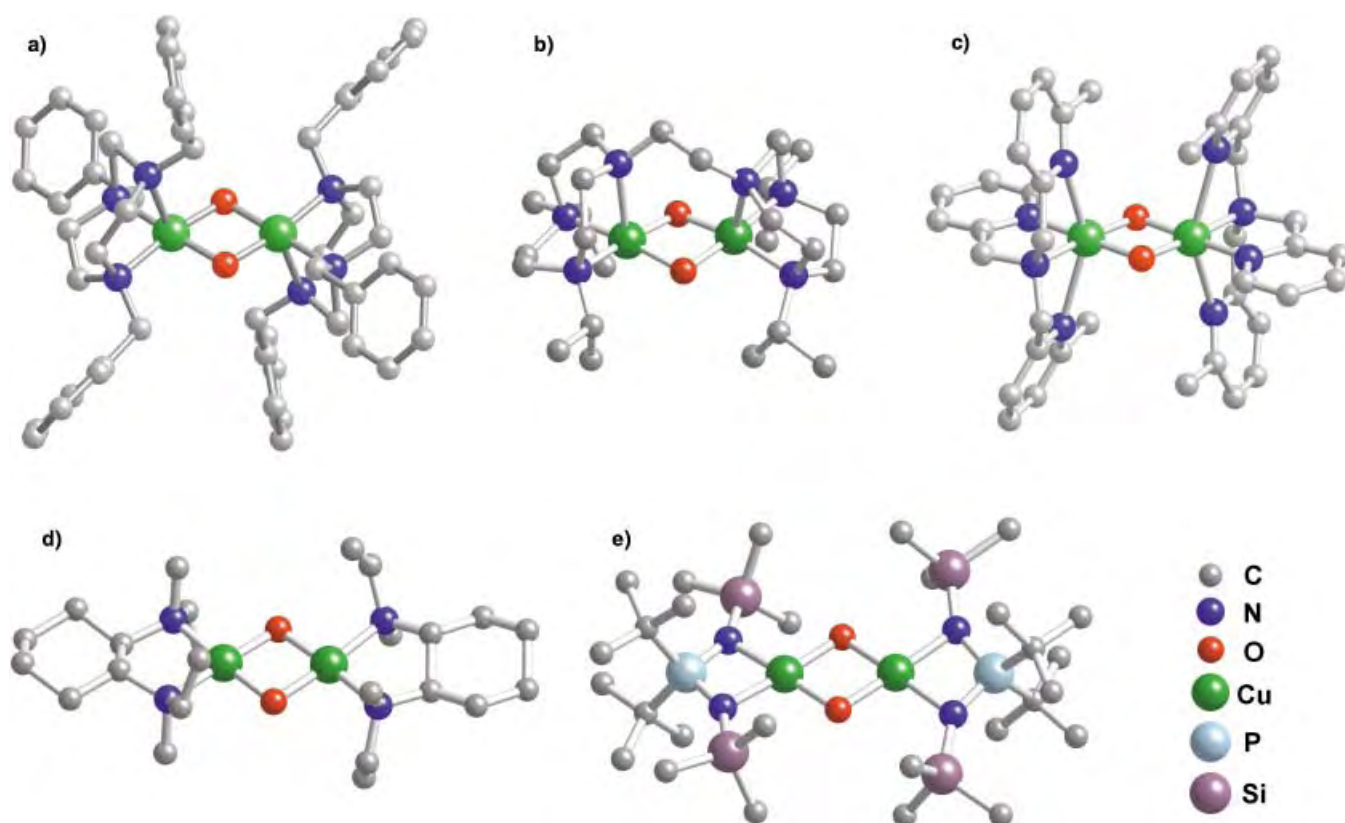


Figure 2. X-ray crystal structures of a) $[(\text{D})_{21}\text{-Bn}_3\text{tacn})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$,^[21, 22] b) $[(\text{D})_{28}\text{-iPr}_4\text{dtne})\text{Cu}_2(\mu\text{-O})_2]^{2+}$,^[23] c) $[(6\text{-Me}_3\text{tpa})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$,^[30] d) $[(\text{Me}_2\text{Et}_2\text{chd})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$,^[26] and e) $[(\text{Bu}_2\text{P}(\text{ntms})_2)_2\text{Cu}_2(\mu\text{-O})_2]$.^[32]

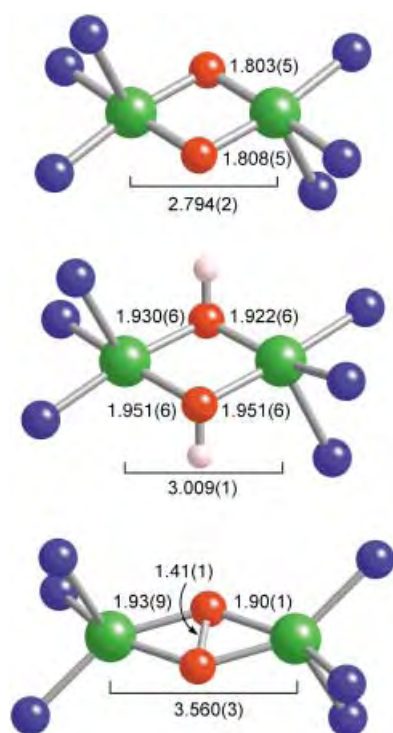


Figure 3. Comparison of prototypical $[\text{Cu}_2^{\text{II}}(\mu\text{-O})_2]^{2+}$ (top), $[\text{Cu}_2^{\text{II}}(\mu\text{-OH})_2]^{2+}$ (middle), and $[\text{Cu}_2^{\text{II}}(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)]^{2+}$ (bottom) cores from the respective X-ray structures of $[(\text{D})_{21}\text{-Bn}_3\text{tacn})_2\text{Cu}_2(\mu\text{-O})_2](\text{SbF}_6)_2$,^[21, 22] $[(i\text{Pr}_2\text{Htacn})_2\text{Cu}_2(\mu\text{-OH})_2](\text{BPh}_4)_2$,^[22] and $[\text{Tp}_2^{\text{Pr}_2}\text{Cu}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)]$.^[58] Selected interatomic distances [Å] are indicated, with estimated standard deviations given in parentheses.

bis(μ -oxo) core is much larger^[59] and this difference is accompanied by a decreased O–O distance indicative of a bond between these atoms.^[58, 60] The metal–ligand bond distances in the $[\text{Cu}_2(\mu\text{-OH})_2]^{2+}$ and $[\text{Cu}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)]^{2+}$ cores are generally longer than in the bis(μ -oxo)dicopper compounds, a fact which is consistent with the Cu_2^{II} assignment for the two former species and Cu_2^{III} for the latter (see Section 5).

3.2. Iron

Figure 4 illustrates features of the cores found in several representative diiron complexes with bridging oxo and/or hydroxo ligands. Only one X-ray structure of a bis(μ -oxo)diiron(III,III) complex, $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_2$, is available.^[42, 43] While its overall topology closely resembles those of the bis(μ -oxo)dicopper and -nickel complexes supported by the same 6-Me₃tpa or similar 6-Me₂tpa ligands (Figure 2),^[15, 30] several unique aspects of the diiron core structure are worth noting (Table 3, entry 11). First, the Fe– μ -O bond lengths differ significantly, with one short bond *trans* to the ligand amine N atom (1.844(3) Å) and a longer bond *trans* to a pyridine donor atom (1.916(4) Å). This pronounced asymmetry in the core ($\Delta r = 0.076$ Å) is mirrored in $[\text{Fe}_2(\mu\text{-OR})_2]^{4+}$ complexes (R = H or alkyl/aryl),^[61] but contrasts with the more similar distances observed in bis(μ -oxo)dimetal compounds with M = Cu, Mn, V, or Cr. The Fe– μ -O distances are notably longer than in diiron(III,III) complexes with a

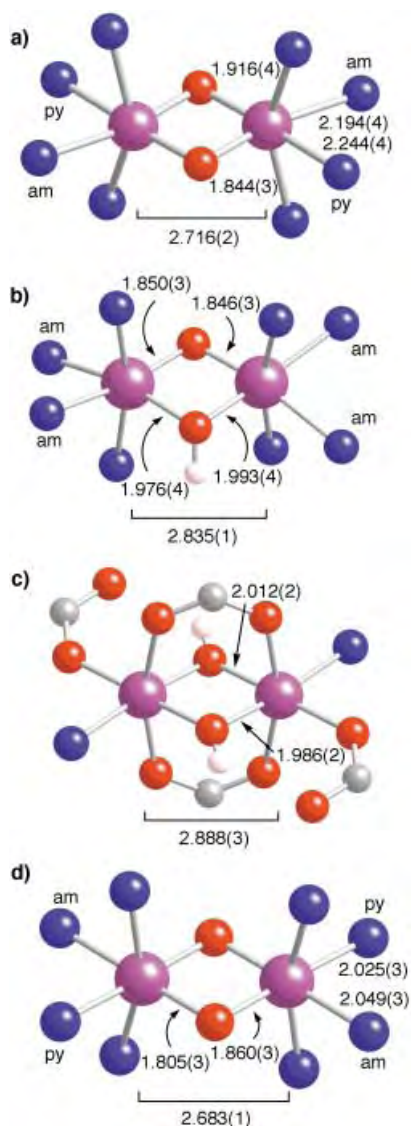


Figure 4. Comparison of the cores a) $[\text{Fe}_2^{\text{II}}(\mu\text{-O})_2]^{2+}$, b) $[\text{Fe}_2^{\text{III}}(\mu\text{-O})(\mu\text{-OH})]^{3+}$, c) $[\text{Fe}_2^{\text{III}}(\mu\text{-OH})_2(\text{O}_2\text{CR})_2]^{2+}$, and d) $[\text{Fe}_2^{\text{III}}\text{Fe}^{\text{IV}}(\mu\text{-O})_2]^{3+}$ from the respective X-ray structures of $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_2$,^[42, 43] $[(\text{bpeen})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})](\text{ClO}_4)_3$,^[43] $[(\text{py})_2(\text{O}_2\text{CAr})_2\text{Fe}_2(\mu\text{-OH})_2(\mu\text{-O}_2\text{CAr})_2]$ ($\text{O}_2\text{CAr} = 2,6\text{-ditolylbenzoate}$),^[57] and $[(5\text{-Et}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_3$.^[49] Selected interatomic distances [Å] are indicated, with estimated standard deviations in parenthesis. The blue N atoms labeled “am” and “py” are amine and pyridyl donors, respectively.

single $\mu\text{-oxo}$ bridge (range 1.73–1.83 Å),^[62] an observation that may be rationalized by invoking lessened Lewis acidity of the Fe^{III} ions as a result of the second $\mu\text{-oxo}$ bridge and greater steric interactions inherent in the compact $[\text{Fe}_2(\mu\text{-O})_2]^{2+}$ core. This core is contracted compared to that of protonated forms^[43, 61] (in the absence of additional bridges^[54, 56, 57]), as reflected in the trend in $\text{Fe}\cdots\text{Fe}$ distances: $[\text{Fe}_2(\mu\text{-O})_2]^{2+} < [\text{Fe}_2(\mu\text{-OH})(\mu\text{-O})]^{3+} < [\text{Fe}_2(\mu\text{-OH})_2]^{4+}$ (Table 3, entries 11–14). A similar trend has been noted for a series of Mn^{III} complexes.^[63] In addition, the $\text{Fe}-\mu\text{-O}-\text{Fe}$ angles are smaller than the $\text{Fe}-\mu\text{-OH}-\text{Fe}$ ones. Finally, it is noteworthy in the current context that a recently prepared bis($\mu\text{-oxo}$)digallium(III,III) complex supported by bidentate β -diketiminato

ligands has a particularly short metal–metal distance and acute Ga–O–Ga angle (Table 3, entry 21).^[64]

Consistent with its higher oxidation level and its spin state, metal–ligand bond distances in the low-spin diiron(III,IV) complex $[(5\text{-Et}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_3$ are shorter than in the high-spin bis($\mu\text{-oxo}$)diiron(III,III) compound (Table 3, entries 9–11).^[49] Nonetheless, the $\text{Fe}\cdots\text{Fe}$ distances and $\text{Fe}-\text{O}-\text{Fe}$ angles are similar in the two compounds, again attesting to the relative structural invariance of the bis($\mu\text{-oxo}$)dimetal unit. Another similarity is the asymmetry in the core $\text{Fe}-\mu\text{-O}$ distances [$\Delta r = 0.055$ Å for the diiron(III,IV) case], further corroborating the aforementioned generality of this feature in diiron(III and/or IV) systems.

4. Spectroscopic Signatures

In the absence of X-ray crystallographic information, the presence of an $M_2(\mu\text{-O})_2$ core structure may be deduced by spectroscopic methods, of which the most directly diagnostic are extended X-ray absorption fine structure (EXAFS) and resonance Raman (rR) spectroscopies. The EXAFS region (above the edge jump) of an X-ray absorption spectrum of a metal complex contains information regarding the nature of the atoms surrounding the metal center and their distances from the metal center.^[65] The r' -space EXAFS spectrum of a complex with an $M_2(\mu\text{-O})_2$ core generally contains two prominent features,^[17, 21, 22, 28, 34, 46, 48b, 49, 66] exemplified for $M = \text{Fe}$ in Figure 5 a, b. One is typically found at $r \approx 2$ Å and corresponds to the first coordination sphere (white arrow). This feature consists of the short (1.8 Å) M–O bonds that make up the core and the longer (2.0–2.1 Å) M–O/N bonds of the terminal ligands. Because of their > 0.2 Å difference, these two shells can usually be resolved in the EXAFS fitting protocol. The second feature is typically found at $r = 2.6$ –2.9 Å (black arrow) and is associated with scattering between the two metal centers in the $M_2(\mu\text{-O})_2$ core. Because of the presence of the two oxo bridges, the metal–metal distance is constrained to be less than 3 Å and the M–O–M angle approaches 90° . These properties distinguish the $M_2(\mu\text{-O})_2$ core from other dinuclear motifs found in metalloproteins such as $M_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)$, $M_2(\mu\text{-O})(\text{O}_2\text{CR})_x$, and $M_2(\text{O}_2\text{CR})_x$ cores, which usually have metal–metal distances greater than 3 Å and much larger M–O–M angles. Furthermore, independent movements of the two metal ions in the $M_2(\mu\text{-O})_2$ unit are significantly limited. Thus, their motions are highly correlated, which leads to an intensity for the outer-sphere feature (black arrow) that is comparable to that arising from the first coordination-sphere atoms. This effect is operative even when the oxo bridges are protonated (Figure 5c and d). Note however that no outer-sphere feature is readily discerned for the paddlewheel complex $[\text{Fe}_2(\text{O}_2\text{CtBu})_4(\text{pyridine})_2]$ (Figure 5e), despite the fact that it has an $\text{Fe}-\text{Fe}$ distance shorter than $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})]^{2+}$ (Figure 5c). The absence of the outer-sphere peak may be rationalized by the presence of a much less rigid core structure in $[\text{Fe}_2(\text{O}_2\text{CtBu})_4(\text{pyridine})_2]$, in which the metal ions are held together only by flexible, bidentate carboxylate bridges. Based on the examples shown, the presence of at least two single-atom

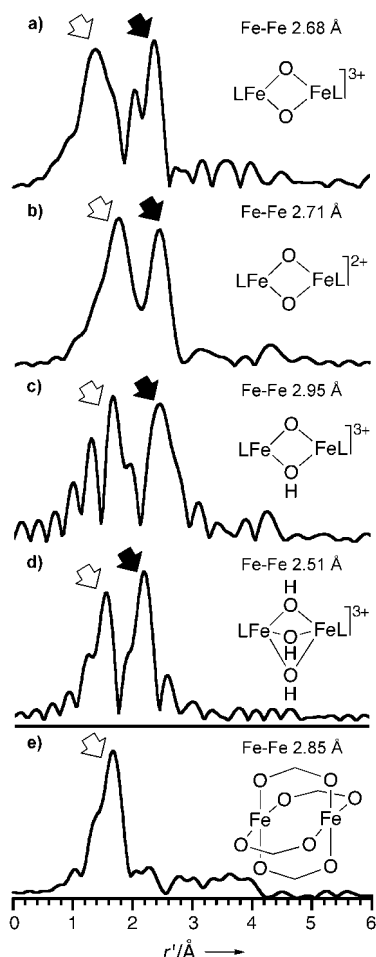


Figure 5. EXAFS spectra plotted in r' space ($r \approx r' + 0.4$) for a) $[\text{Fe}_2(\mu\text{-O})_2(5\text{-Me}_3\text{tpa})_2]^{3+}$, b) $[\text{Fe}_2(\mu\text{-O})_2(6\text{-Me}_3\text{tpa})_2]^{2+}$, c) $[\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})(6\text{-Me}_3\text{tpa})_2]^{3+}$, d) $[\text{Fe}_2(\mu\text{-OH})_2(\text{Me}_3\text{tacn})_2]^{2+}$, e) $[\text{Fe}_2(\text{O}_2\text{CR})_4(\text{pyridine})_2]$. First-shell features are indicated by the white arrow and the second-shell features (Fe–Fe scattering) are noted with a black arrow (a–d). Adapted with permission from ref. [49].

bridges are necessary to give rise to the strong intensity of the outer-sphere metal scattering. These principles also apply to complexes with $\text{M} = \text{Cu}$ and Ni .^[17, 20, 22, 28, 34] Thus, such an intense outer sphere feature is a convenient spectroscopic tool to determine the presence of an $\text{M}_2(\mu\text{-O})_2$ core.

The $\text{M}_2(\mu\text{-O})_2$ core also exhibits characteristic oxygen-isotope-sensitive features in vibrational spectra that are useful for identification purposes. Such vibrations are observed in Raman spectra upon excitation into an electronic absorption band having oxo $\rightarrow$ metal charge-transfer (CT) character (Section 5).^[67–69] Simple symmetry considerations indicate that the $\text{M}_2(\mu\text{-O})_2$ core has six core vibrations, three of which have the appropriate symmetry to be Raman active (Figure 6). In practice however, only the totally symmetric (A_g) modes are observed. Thus, for complexes with D_{2h} and C_{2h} (with the z axis in the M_2O_2 plane) symmetry, there are two vibrations with A_g symmetry; one involving significant M–O stretching called the “breathing” mode and the other a core bending mode. For complexes with C_{2h} symmetry where the z axis is perpendicular to the M_2O_2 plane, there is a third A_g mode designated the “pairwise” stretching mode.

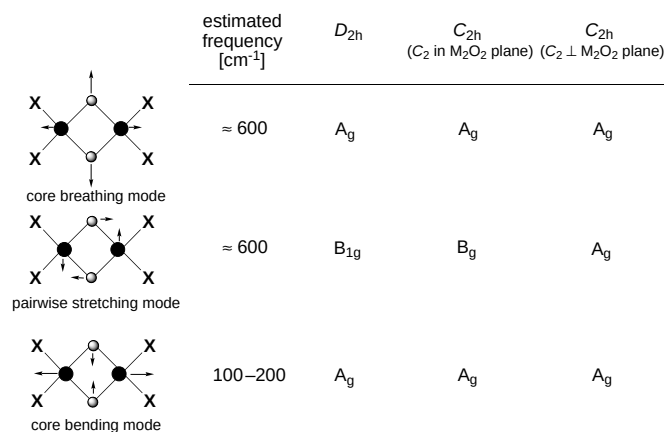


Figure 6. Frequencies and symmetry representations of important vibrational modes of bis(μ -oxo)dimetal cores in different point groups.

Complexes with $\text{Fe}_2(\mu\text{-O})_2$ cores exhibit a prominent oxygen-isotope-sensitive Raman feature at 650–690 cm^{-1} .^[67] Our understanding of this vibration derives from the large amount of structural and Raman information available for oxo-bridged diiron complexes.^[62, 70] An Fe–O–Fe unit has two stretching vibrations that arise from the two Fe–O bonds. The extent to which the two vibrations are coupled depends on the M–O–M angle, with the strongest coupling found for linear Fe–O–Fe complexes. In these complexes, the symmetric combination $\tilde{\nu}_{\text{sym}}(\text{Fe-O-Fe})$ is observed in their Raman spectra at around 350 cm^{-1} and the asymmetric combination $\tilde{\nu}_{\text{asym}}(\text{Fe-O-Fe})$ is observed at approximately 850 cm^{-1} in their IR spectra, consistent with the respective symmetries of the vibrations and the selection rules associated with the two spectroscopic techniques. As the Fe–O–Fe angle becomes more acute, the coupling interaction weakens and the two vibrations start to converge to a common value.^[70] Figure 7 displays the currently available vibrational data for structurally characterized oxo-bridged diiron complexes (open and closed circles) and demonstrates the correlation between the M–O–M angle and the $\tilde{\nu}_{\text{sym}}(\text{Fe-O-Fe})$ and $\tilde{\nu}_{\text{asym}}(\text{Fe-O-Fe})$ values. Note that at an M–O–M angle of 90°, where the two Fe–O bonds are orthogonal and the two Fe–O vibrations are independent of each other, the $\nu(\text{Fe-O-Fe})$ values approach 650 cm^{-1} . The recent report of a $\nu(\text{Fe-O})$ of 671 cm^{-1} for a mononuclear iron(III)–oxo complex supports this prediction.^[71]

The symmetry of the Fe–O–Fe core plays an important role in determining the intensities of the Fe–O–Fe vibrations in the Raman spectrum. In complexes where the two iron coordination environments are essentially identical, only the allowed $\nu_{\text{sym}}(\text{Fe-O-Fe})$ mode is observed as an intense peak. The forbidden $\nu_{\text{asym}}(\text{Fe-O-Fe})$ mode would at best be observed as a very weak peak, so the intensity ratio $I_{\text{asym}}/I_{\text{sym}}$ would be close to zero. As the asymmetry of the Fe–O–Fe unit increases, the $\nu_{\text{asym}}(\text{Fe-O-Fe})$ mode becomes more easily observed in the Raman spectrum. For example, for the tpa complexes with a $(\mu\text{-oxo})(\mu\text{-carboxylato})$ diiron(III,III) core such as the $[(\text{tpa})_2\text{Fe}_2(\mu\text{-O})(\text{O}_2\text{CCH}_3)]^{3+}$ ion the $I_{\text{asym}}/I_{\text{sym}}$ ratio is around 0.2 because the oxo bridge is *trans* to the N atom of a pyridine group on one metal center and *trans* to an amine group N atom on the other.^[72] A more dramatic example of an

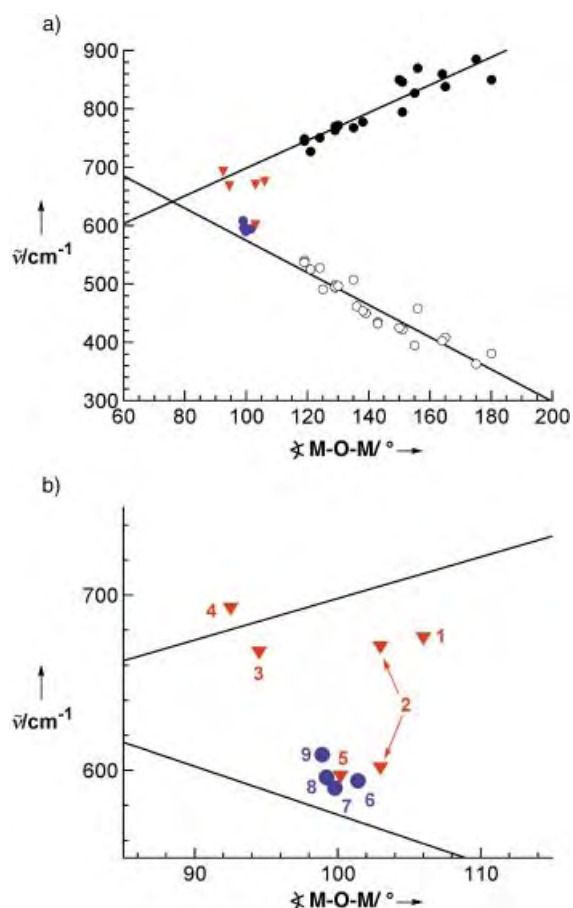


Figure 7. a) Plot of M-O-M angle versus $\tilde{\nu}_{\text{sym}}$ (○) and $\tilde{\nu}_{\text{asym}}$ (●) for a series of complexes containing Fe-O-Fe cores. Data for structurally characterized complexes with $\text{Fe}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})$ cores are represented by ▼ and for $\text{Cu}_2(\mu\text{-O})_2$ cores by ●. b) Expanded region of the plot in Figure 7a with labels referring to specific vibrations and complexes: **1**: ν_{asym} of $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})](\text{ClO}_4)_3$, **2**: ν_{asym} (top) and ν_{sym} (bottom) of $[(4,6\text{-Me}_6\text{tpa})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})](\text{ClO}_4)_3$, **3**: ν_{asym} of $[(5\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_3$, **4**: ν_{asym} of $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2](\text{ClO}_4)_2$, **5**: ν_{sym} of $[(\text{bpeen})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})](\text{ClO}_4)_3$, **6**: $[(\text{D})_{21}\text{-Bn}_3\text{tacn})_2\text{Cu}_2(\mu\text{-O})_2](\text{ClO}_4)_2$, **7**: $[(6\text{-Me}_3\text{tpa})_2\text{Cu}_2(\mu\text{-O})_2](\text{PF}_6)_2$, **8**: $[(\text{D})_{28}\text{-iPr}_4\text{dtne})\text{Cu}_2(\mu\text{-O})_2](\text{ClO}_4)_2$, **9**: $[(\text{Me}_2\text{Et}_2\text{chd})_2\text{Cu}_2(\mu\text{-O})_2](\text{CF}_3\text{SO}_3)_2$. Adapted with permission from refs. [43, 67, 70], with additional data from ref. [67–69].

asymmetric Fe-O-Fe core is that of the $[(\text{N}5)\text{Fe-O-FeCl}_3]^+$ ion,^[73] which features an octahedral metal center on one side and a tetrahedral metal center on the other. For this complex, the $I_{\text{asym}}/I_{\text{sym}}$ ratio jumps to 4.2. The $\text{Fe}^{\text{II}}\text{-O-Fe}^{\text{III}}$ unit of the mixed-valent $[(\text{Me}_3\text{tacn})_2\text{Fe}_2(\mu\text{-O})(\text{O}_2\text{CR})_2]^+$ compound may be considered an extreme example of an asymmetric Fe-O-Fe core,^[74] and only the $\nu_{\text{asym}}(\text{Fe-O-Fe})$ mode is observed. Clearly, the Raman properties of the Fe-O-Fe core serve as sensitive probes of its symmetry properties.

The entries at low M-O-M angle in Figure 7 (red triangles, labeled specifically in Figure 7b) comprise compounds with diamond-shaped diiron cores; the introduction of a second single-atom bridge restricts the size of the M-O-M angle to 100° or less. For complexes with an $\text{Fe}_2(\text{O})(\text{OH})$ core, the M-O-M angle is about 100°. Interestingly the bpeen (for structure see Scheme 1) complex has its $\nu(\text{Fe-O-Fe})$ feature at 596 cm^{-1} , while the 6-Me₃tpa complex has its feature at

675 cm^{-1} .^[43] As indicated in Figure 7, the feature for the bpeen complex falls near the line for $\nu_{\text{sym}}(\text{Fe-O-Fe})$, while that for the 6-Me₃tpa complex is closer to the line for $\nu_{\text{asym}}(\text{Fe-O-Fe})$. The difference between the two complexes can be rationalized by considering their structures. The bpeen complex has a symmetric Fe-O-Fe unit with the oxo bridge *trans* to amine nitrogen atoms on both irons, so it displays an intense $\nu_{\text{sym}}(\text{Fe-O-Fe})$ band. On the other hand, the oxo bridge is *trans* to an amine nitrogen atom on one iron and *trans* to a pyridine nitrogen atom on the other in the 6-Me₃tpa complex, which results in greater intensity for $\nu_{\text{asym}}(\text{Fe-O-Fe})$. Consistent with the fact that they have structures quite similar to that of $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2]^{2+}$, the high valent $[\text{L}_2\text{Fe}_2\text{O}_2]^{3+}$ complexes (L = tpa, 5-Me₃tpa, and 5-Et₃tpa) each exhibit just one major Raman peak with values that fall on the $\nu_{\text{asym}}(\text{Fe-O-Fe})$ line. Thus, the correlation in Figure 7 applies not only to oxo-bridged diiron(III,III) complexes but also to oxo bridged $\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}$ and $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ complexes as well.

The fact that the Raman features of $\text{Fe}_2(\mu\text{-O})_2$ complexes fit well into the correlation of $\nu(\text{Fe-O-Fe})$ with M-O-M angle raises the question of whether the observed vibration is triatomic or is instead associated with a mode of the entire tetraatomic core. This question may be probed by introducing just one ¹⁸O isotope into the Fe_2O_2 core. The assignment of the Raman feature to a triatomic vibration would be confirmed by the observation of two features in the spectrum of the mixed-labeled complex arising from $\nu(\text{Fe-}^{16}\text{O-Fe})$ and $\nu(\text{Fe-}^{18}\text{O-Fe})$ vibrations, with relative intensities reflecting the populations of the two isotopomers (e.g., equal intensities for a 1:1 ratio of ¹⁶O:¹⁸O). In contrast, a vibration that is tetraatomic in nature would exhibit a single feature with a value intermediate between the two ¹⁶O¹⁶O- and ¹⁸O¹⁸O-labeled extremes. For $[(\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2]^{3+}$,^[67] the ¹⁶O¹⁶O isotopomer exhibits a Raman peak at 666 cm^{-1} that shifts 28 cm^{-1} to lower energy in the ¹⁸O¹⁸O isotopomer. When ¹⁸O is incorporated into only one oxygen atom of the $\text{Fe}_2(\mu\text{-O})_2$ core, a single peak with an isotope shift of 22 cm^{-1} is observed. Thus, the iron–oxo vibration observed for $[(\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2]^{3+}$ and related complexes derives from motion of the entire tetraatomic core.

Assignment of the 650–690 cm^{-1} band for the $\text{Fe}_2(\mu\text{-O})_2$ complexes rests on their having C_{2h} symmetry with the C_2 axis perpendicular to the M_2O_2 core, such that there are two modes with totally symmetric A_g representations that are thus Raman allowed (Figure 6). One, designated the “breathing” mode, is analogous to the $\nu_{\text{sym}}(\text{Fe-O-Fe})$ band of the triatomic Fe-O-Fe complexes. The other, designated the “pairwise” mode, is analogous to $\nu_{\text{asym}}(\text{Fe-O-Fe})$. Normal coordinate analysis predicts both modes to be at similar frequencies, but the pairwise mode assignment is favored on the basis of several arguments.^[67] There appears to be a weaker feature, observed at 655 cm^{-1} as a low-energy shoulder of the 666 cm^{-1} peak in the tpa complex, which is tentatively assigned as the breathing mode.

Similar considerations apply to the Raman spectra of complexes with $\text{Cu}_2(\mu\text{-O})_2$ cores.^[28, 68, 69] Those with symmetric bidentate ligands such as, $\text{R}_2\text{R}'_2\text{chd}$, $\text{R}_1^1\text{R}_2^2\text{eda}$, and $\text{R}_1^1\text{R}_2^2\text{pda}$ have D_{2h} core symmetry and exhibit two core vibrations (Figure 6). The Raman data for the complex $[(\text{Me}_2\text{Et}_2\text{chd})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$ is illustrative (Figure 8).^[68] An intense

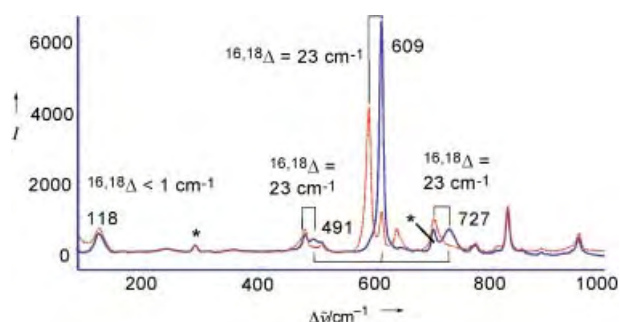


Figure 8. Resonance Raman spectra of $[(\text{Me}_2\text{Et}_2\text{chd})_2\text{Cu}_2(\mu\text{-O})_2](\text{CF}_3\text{SO}_3)_2$ in CH_2Cl_2 , derived from $^{16}\text{O}_2$ (blue) and $^{18}\text{O}_2$ (red). Asterisks denote solvent peaks. Adapted with permission from ref. [68].

feature at 609 cm^{-1} corresponds to the core breathing mode; upon ^{18}O substitution it moves to lower energy by 24 cm^{-1} , in close agreement with the calculated value of 28 cm^{-1} . This intense feature is flanked by two much weaker features separated from the central peak by 118 cm^{-1} that move to lower energy by the same amount as the central feature when ^{18}O is incorporated. Examination of the low-frequency region reveals a feature at 118 cm^{-1} , which is assigned to the core bending mode. Thus, the features flanking the intense 609 cm^{-1} peak are combination and difference bands of the fundamental core breathing and core bending modes. Complexes of the other symmetric diamine ligands exhibit the same features at comparable energies. The fact that the two fundamental modes exhibit frequencies that are essentially independent of the nature of the ligand emphasizes the notion that these are indeed vibrations of the $\text{Cu}_2(\mu\text{-O})_2$ core.

Replacement of the supporting diamines in the bis(μ -oxo)dicopper complexes with tridentate R_3tacn ligands lowers the point-group symmetry of the complexes to C_{2h} , as the copper ions adopt a square pyramidal geometry. Although the principal axis in these cases is coincident with the O–O axis, the symmetry designations for the core vibrations remain unchanged, so the same two totally symmetric Raman modes found for the D_{2h} complexes are expected for these C_{2h} complexes.^[69] Indeed, all the R_3tacn complexes exhibit an intense ^{18}O isotope-sensitive vibration near 600 cm^{-1} that is assigned to the core breathing mode. However, no effort was made to observe the core bending mode in the low-frequency region. A notable difference between the data acquired for the R_3tacn and diamine complexes is an apparent sensitivity of the core breathing mode of the former to the mass of the supporting ligand alkyl substituents, with larger energy decreases as the mass of the alkyl substituent increases.

In $\text{Cu}_2(\mu\text{-O})_2$ complexes with unsymmetric bidentate N-donor ligands the core symmetry also is C_{2h} , but the principal axis is perpendicular to the Cu_2O_2 core. For such complexes, both breathing and pairwise stretching modes belong to the totally symmetric A_g representation, which leads to the expectation of two observable features in the Raman spectrum. Indeed, two ^{18}O isotope-sensitive Raman features are observed in the 600 cm^{-1} region for the complexes $[(\text{EtPhPy})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$ and $[(\text{ArPyNET}_2)_2\text{Cu}_2(\mu\text{-O})_2]$.^[25, 27] The appearance of two Cu–O stretching peaks is reminiscent of the two $\nu(\text{Fe-O})$ features observed in the Raman spectra of Fe–O–

Fe complexes with similarly unsymmetric ligands, as discussed above.^[43] However, another complex which belongs to this class, $[(6\text{-Me}_2\text{tpa})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$, exhibits only one ^{18}O isotope-sensitive Raman feature in the 600 cm^{-1} region. The appearance of only one peak may be rationalized by the crystal structure of this complex, which shows a Cu_2O_2 core with four Cu–O bonds nearly equal in length, so the pairwise mode may not have much intensity. Unfortunately, X-ray crystal structures are not available for the two complexes that exhibit both core breathing and pairwise stretching modes.

When the core breathing modes observed for the Cu_2O_2 complexes are placed on the plot in Figure 7 (blue circles), they essentially fall on the $\nu_{\text{sym}}(\text{M-O-M})$ line, which is consistent with the notion that the core breathing mode is the tetranuclear equivalent of the symmetric M–O–M stretching vibration. It may be surprising that the correlation derived from a database of iron compounds should also apply to copper complexes. Separate analysis of the latter is not possible because there is no database available for mono-oxo bridged dicopper complexes; few of these complexes exist,^[18] none have been characterized structurally, and no Raman data have been reported. Nevertheless, there are a number of $\text{Fe}^{\text{III}}\text{-O-Cu}^{\text{II}}$ complexes that have been synthesized to model the dioxygen binding and activation site of cytochrome *c* oxidase.^[18a,b] One of these exhibits an Fe–O–Cu angle of 178° and a $\tilde{\nu}_{\text{asym}}(\text{Fe-O-Cu})$ at 855 cm^{-1} ,^[75] in good agreement with the correlation in Figure 7. Thus, the differences in the atomic weights of Fe and Cu and in the relative strengths of the M–O bonds appear not to be large enough to affect the correlation in Figure 7 significantly.

In summary, EXAFS and resonance Raman spectroscopy represent two valuable tools that may be used to determine whether an $\text{M}_2(\mu\text{-O})_2$ core is present in a sample. Indeed, these spectroscopic signatures were recognized in the EXAFS and Raman spectra of $[(\text{R}_3\text{tacn})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$ and $[(\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2]^{3+}$ complexes prior to their characterization by X-ray crystallography.^[20, 48] Similar approaches have been used to determine whether an $\text{M}_2(\mu\text{-O})_2$ core is present in the reactions of other dicopper and diiron complexes with O_2 or H_2O_2 .^[28]

5. Electronic Structures

Not surprisingly, despite their similar geometric and vibrational properties the bis(μ -oxo)dimetal cores comprising iron and copper have differing electron inventories that result in divergent electronic structures. These structures have been probed by both experimental and theoretical methods. The $\text{Cu}_2(\mu\text{-O})_2$ complexes are best characterized as having Cu^{III} ions bridged by two oxide ions. The Cu^{III} oxidation state description is supported by a bond valence sum (BVS) analysis of the crystallographic data^[22, 76] and an analysis of X-ray absorption pre-edge energies.^[77] In the BVS analysis, values for the copper-ion oxidation level consistently much larger than +2 were obtained when the structural data were analyzed using parameters derived from Cu^{II} complexes, while values close to +3 were obtained using parameters

associated with known Cu^{III} complexes. More direct information was gleaned from the X-ray absorption edges. Through an analysis of a large series of complexes, a clear distinction between those that contain Cu^{II} and those with Cu^{III} was drawn. While Cu^{II} complexes exhibit a $1s \rightarrow 3d$ pre-edge peak at 8979 ± 0.5 eV that is quite insensitive to changes in the ligand environment, the corresponding feature for Cu^{III} complexes is observed at 8981 ± 0.5 eV, consistently 2 eV higher in energy than its Cu^{II} counterpart. This shift to higher energy is as expected because of the higher nuclear charge of Cu^{III} centers that makes it more difficult to excite a core electron.

Analysis of magnetic and absorption spectroscopic data^[68] in conjunction with a number of theoretical studies^[22, 29, 32, 78, 79] have led to a detailed picture of the bonding within the $\text{Cu}_2(\mu\text{-O})_2$ core. Complexes with this core are diamagnetic, which is consistent with the d^8 electronic configuration of Cu^{III} and the tetragonal nature of the coordination sphere. In their optical absorption spectra, these complexes are characterized by two intense bands near 300 and 400 nm ($\epsilon \sim 10\,000\text{--}25\,000\text{ M}^{-1}\text{cm}^{-1}$). Attribution of the longer wavelength band to an oxo $\rightarrow$ copper(III) CT transition is supported by its intensity and by resonance Raman excitation profiles, which show close correlation of the band shape for the 400 nm absorption with the ^{18}O -sensitive-band intensities in the Raman spectrum.^[68] More detailed assignments of the absorption features, as well as other electronic

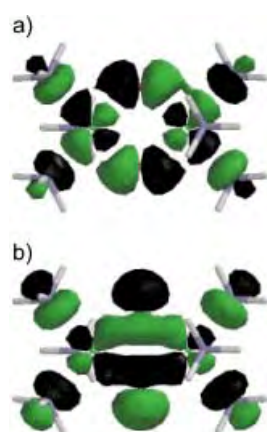


Figure 9. Key filled (a) and empty (b) frontier molecular orbitals calculated for $[(\text{NH}_3)_6\text{Cu}_2(\mu\text{-O})_2]^{2+}$. Adapted with permission from ref. [11a].

structural insights, have come from computations that have defined the core bonding in molecular orbital (MO) terms. Two key frontier orbitals calculated for the model $[(\text{NH}_3)_6\text{Cu}_2(\mu\text{-O})_2]^{2+}$ are shown in Figure 9;^[22, 78] similar orbitals have been calculated for molecules with similar N-donor ligands at varying levels of theory.^[68, 79] The filled, lower energy MO (Figure 9a) comprises oxygen p orbitals that are antibonding with respect to each other, but which have strong bonding interactions with the Cu $d_{x^2-y^2}$ orbitals (e.g. high covalency). Antibonding interactions between all of the metal and oxygen orbitals are present in the

empty, higher lying MO (Figure 9b). Electronic excitation from the filled to the empty MO is thought to give rise to the lower energy optical transition (≈ 400 nm),^[68] with the intensity of this band arising from the high degree of metal–ligand bond covalency illustrated by the MO drawings. This large covalency also accounts for the strong enhancement observed for the Cu–O vibrations in resonance Raman spectra (Section 4). The higher energy UV absorption feature corresponds to one of similar energy and intensity found in $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{dicopper(II,II)}$ units (peroxo $\pi_\sigma^* \rightarrow \text{Cu} d_{xy}$ LMCT)^[80] and has been assigned analogously.^[68]

Because Fe^{III} and Fe^{IV} centers can adopt different spin states, the electronic structures of the $\text{Fe}_2(\mu\text{-O})_2$ complexes are more varied than those of their copper counterparts. The diiron(III) complexes with $\text{Fe}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})$ cores characterized to date all have high-spin Fe^{III} ions and they exhibit electronic spectra similar to those of $(\mu\text{-oxo})\text{diiron(III,III)}$ complexes. The latter compounds exhibit two moderately intense absorption features in the 500–700 nm region ($\epsilon \approx 200\text{--}500\text{ M}^{-1}\text{cm}^{-1}$) that have been assigned to transitions that have both LMCT and ligand-field character.^[81, 82] Corresponding features for the $\text{Fe}_2(\mu\text{-O})_2$ and $\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})$ complexes are observed at 500 and 800 nm, with the latter band significantly red-shifted as a result of the acute Fe–O–Fe angles found in these cores.^[43] Excitation into the 500 nm band gives rise to the core vibrations in the Raman spectra discussed in Section 4.

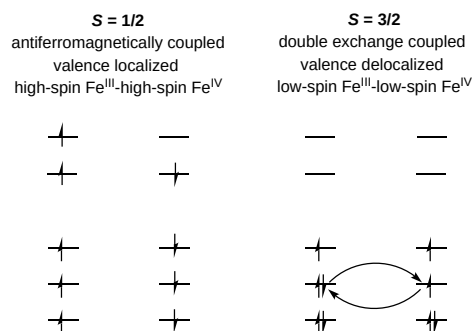
Like the $(\mu\text{-oxo})\text{diiron(III,III)}$ complexes, the high-spin iron(III) centers in the $[\text{Fe}_2(\mu\text{-O})_2]^{2+}$ and $[\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})]^{3+}$ cores are antiferromagnetically coupled, but the strengths of the coupling interactions differ. Compounds with $(\mu\text{-oxo})\text{diiron(III,III)}$ units have J values that range from 180 cm^{-1} to 250 cm^{-1} ($\mathbf{H} = J\mathbf{S}_1\mathbf{S}_2$) and that appear to be rather insensitive to Fe–O–Fe angles between 120° and 180° .^[62] While introduction of a second efficient exchange pathway in complexes with $[\text{Fe}_2(\mu\text{-O})_2]^{2+}$ and $[\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})]^{3+}$ cores may lead to the expectation of an even stronger coupling interaction, these complexes actually exhibit weaker antiferromagnetic coupling. For example, $J = +110(10)\text{ cm}^{-1}$ for $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})(\mu\text{-OH})]^{3+}$ and $J = +54(8)\text{ cm}^{-1}$ for $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-O})_2]^{2+}$.^[42] These smaller J values have been ascribed to the rather small Fe–O–Fe angles ($90\text{--}105^\circ$) and the longer Fe– μ -O bonds associated with these complexes. Indeed, the J values found for these complexes fit well into a published correlation that relates J values to the average Fe– μ -O bond length of the shortest superexchange pathway between two iron(III) ions.^[83] The inclusion of data from these complexes refines and further validates this correlation by providing needed values for complexes with intermediate Fe–O bond lengths.

The electronic properties of the higher valent bis($\mu\text{-oxo})\text{diiron(III,IV)}$ complexes divide them into two subsets, depending on whether the iron ions are high or low spin. Those with high spin iron centers exhibit $S = \frac{1}{2}$ ground states and have Mössbauer spectra consisting of two quadrupole doublets, one with an isomer shift δ of about 0.5 mm s^{-1} , characteristic of high-spin Fe^{III} centers, and the other with a δ value of around 0.1 mm s^{-1} , associated with Fe^{IV} centers (Table 4).^[84] Consistent with the high-spin assignment, the hyperfine parameters of the Fe^{III} ion are isotropic, while those of the Fe^{IV} ion exhibit significant anisotropy. The $S = \frac{1}{2}$ state thus must arise from the antiferromagnetic coupling of $S = \frac{5}{2}$ Fe^{III} and $S = 2$ Fe^{IV} ions (Figure 10, left). Nine out of the ten d orbitals of the diiron(III,IV) center are magnetic, and superexchange causes antiparallel alignment, which can readily occur through single-atom bridges. The $S = \frac{1}{2}$ spin state is also manifested in the EPR spectra as an isotropic signal at $g = 2$ at X-band frequency.^[50, 51, 53, 54]

The other subset of bis($\mu\text{-oxo})\text{diiron(III,IV)}$ complexes consists of three closely related compounds with $\text{L} = \text{tpa}$, 5- $\text{Me}_3\text{-tpa}$, or 5- $\text{Et}_3\text{-tpa}$ that have $S = \frac{3}{2}$ ground states, as

Table 4. Mössbauer parameters for diiron(III,IV) complexes.

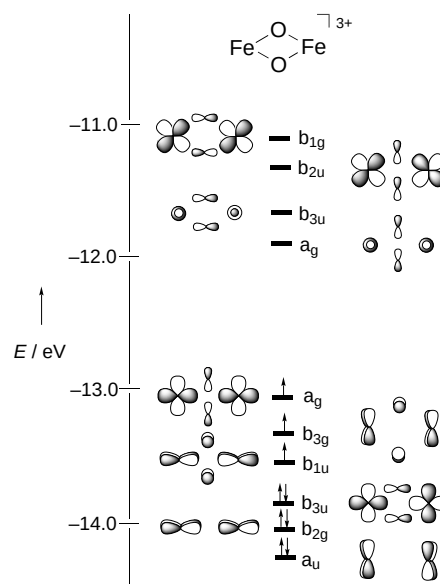
L or protein	Electronic description	$\delta(\text{Fe}^{\text{IV}})$	$\Delta E_{\text{O}}(\text{Fe}^{\text{IV}})$	$\delta(\text{Fe}^{\text{III}})$	$\Delta E_{\text{O}}(\text{Fe}^{\text{III}})$	Ref.
5-Me ₃ -tpa	valence delocalized $S = 3/2$	0.14(2)	+ 0.49(3)	–	–	[48b]
6-Me ₃ -tpa	valence localized $S = 1/2$	0.10	1.14	0.50	1.3	[51, 53]
6-Me-tpa	valence localized $S = 1/2$	0.08(3)	0.5(1)	0.48	1.6(2)	[50]
Ar ¹⁰⁰ CO ₂	valence localized $S = 1/2$	0.12	0.6	0.55	1.1	[54]
RNR R2-X	valence localized $S = 1/2$	0.26(4)	– 0.6(1)	0.56(3)	– 0.9(1)	[84a]
MMOH-Q _x	valence localized $S = 1/2$	0.14(6)	– 0.6(1)	0.48(6)	– 0.9(1)	[84b]

Spin States of $[\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}(\text{O})_2]^{3+}$ ComplexesFigure 10. Overview of magnetic interactions and spin states in $[\text{L}_2\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}(\text{O})_2]^{3+}$ complexes.

indicated by EPR spectra with g values at 4.3, 3.7, and 2.^[48b] The metal ions in the $\text{Fe}_2(\mu\text{-O})_2$ core supported by 5-Et₃-tpa were shown by X-ray crystallography to be in essentially equivalent environments.^[49] Mössbauer spectra of the series of complexes consist of only one quadrupole doublet ($\delta \approx 0.14 \text{ mm s}^{-1}$) showing that the $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ center is valence delocalized.^[48] The $S = 3/2$ ground state derives from the parallel alignment of the single spin on the $S = 1/2$ Fe^{III} center and the two spins of the $S = 1$ Fe^{IV} ions that is enforced by a double exchange mechanism (Figure 10, right).

Density functional theory (DFT) calculations have provided an MO description that rationalizes the observed $S = 3/2$ ground state.^[85] As shown in Figure 11, the frontier MOs of $[\text{Fe}_2(\mu\text{-O})_2(\text{tpa})_2]^{3+}$ with predominant metal 3d character consist of two groups well separated in energy. The low-energy set comprises six MOs derived from various combinations of the metal t_{2g} orbitals. Filling these six MOs with nine 3d electrons following Hund's rule results in the observed $S = 3/2$ ground state, consistent with the low-spin description implied by the experimental data. Mulliken analysis of the unpaired spin populations show that the three unpaired electrons are fully localized on the $[\text{Fe}_2(\mu\text{-O})_2]^{3+}$ core and are distributed between the iron and the oxygen atoms in a 4:1 ratio. The fact that neither the iron nor the oxygen atoms have integral spin populations indicates significant covalency in the bonding within the $[\text{Fe}_2(\mu\text{-O})_2]^{3+}$ unit.

The valence delocalized $[\text{L}_2\text{Fe}_2(\mu\text{-O})_2]^{3+}$ complexes were first observed because of their characteristic green color arising from an intense visible absorption band at 616 nm ($\epsilon \sim 5000 \text{ M}^{-1} \text{ cm}^{-1}$).^[48] Since oxo $\rightarrow$ iron CT transitions for oxo-bridged diiron complexes are usually found in the near UV region,^[81, 82] such an intense band at low energy is atypical and hinted at the unusual valence delocalized electronic structure

Figure 11. Frontier molecular orbitals of the $S = 3/2$ $[\text{Fe}_2(\mu\text{-O})_2]^{3+}$ core, with the indicated irreducible representations indicated for the D_{2h} point group. Adapted with permission from ref. [85].

that was subsequently established. The sharpness of this band and its insensitivity to solvent argue against a LMCT designation and support its assignment as an intervalence (metal-to-metal) transition.^[48b]

To summarize, the parent tpa ligand and its two 5-alkyl substituted derivatives give rise to valence delocalized $S = 3/2$ complexes, while its two 6-methyl substituted derivatives form valence trapped $S = 1/2$ complexes. It is remarkable how the introduction of one 6-methyl group can so dramatically alter the electronic structure of the $[\text{Fe}_2(\mu\text{-O})_2]^{3+}$ core.^[51] Clearly, these results emphasize the important influence of ligand structural features on the physical properties of such metal centers.

6. Reactivity

Two major modes of reactivity are exhibited by the thermally unstable bis(μ -oxo)dicopper and/or -diiron complexes: a) core isomerization, which involves O–O bond formation in a conversion into a $\mu\text{-}\eta^2\text{-}\eta^2$ -peroxo core (Cu) or bridge-to-terminal oxo migration (Fe), and b) oxidation of organic functional groups, in either intra- or intermolecular processes. The core isomerization and hydrocarbon C–H activation reactions are of fundamental importance in oxida-

tions performed by non-heme enzymes or synthetic catalysts, and as a result much effort has been expended to understand associated mechanistic issues.

6.1. Core Isomerization

The separate isolation of $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo- and bis(μ -oxo)dicopper complexes with different supporting N-donor ligands (e.g., $\text{Tp}^{\text{R,R'}}$ versus Bn_3tacn ; Tp = tris(pyrazolyl)hydroborate) suggested that under suitable conditions these two isomeric cores might interconvert in an unprecedented process. Studies of the oxygenation of Cu^{I} complexes of $i\text{Pr}_3\text{tacn}$ a) led to the identification of both peroxo and bis(μ -oxo) isomers supported by the same N-donor ligand and b) provided the first experimental evidence that these particular isomers could indeed participate in a facile equilibrium.^[11, 21] Important evidence included the identification by UV/Vis and resonance Raman spectroscopy of $[(i\text{Pr}_3\text{tacn})_2\text{Cu}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)]^{2+}$ upon performing the low-temperature oxygenation of $[(i\text{Pr}_3\text{tacn})\text{Cu}(\text{CH}_3\text{CN})]^+$ in CH_2Cl_2 and the finding of spectral features arising from the bis(μ -oxo) core when the oxygenation was performed in concentrated THF solutions. Solvent-mixing experiments involving dilution of concentrated CH_2Cl_2 solutions with THF and vice versa resulted in spectral changes indicating transmutation of the isomers.^[21, 39] In acetone, spectral signatures of both forms were seen. These initial discoveries showed that the two cores supported by $i\text{Pr}_3\text{tacn}$ have similar thermodynamic stabilities, such that changes in solvent are sufficient to result in formation of one or the other form. Consistent with the energetic similarity between the isomers, X-ray diffraction and resonance Raman spectroscopic data obtained on crystals isolated from CH_2Cl_2 solution suggested the existence of both forms, compositionally disordered, in the solid state.^[11]

Evidence for a rapid isomerization equilibrium between the compounds supported by $i\text{Pr}_3\text{tacn}$ came from the results of low-temperature stopped-flow kinetics experiments.^[21] The formation of a $\approx 4\text{:}1$ mixture of the peroxo and bis(μ -oxo) isomers from the reaction of $[\text{LCu}(\text{CH}_3\text{CN})]^+$ with O_2 in acetone was found to have a first-order dependence on the concentration of the Cu^{I} complex. Activation parameters (Table 2) are consistent with formation of $[\text{LCu}(\text{O}_2)]^+$ in the rate-determining step. In addition, the spectral features of each isomer grew at identical rates at a range of temperatures (-83°C to -50°C). Identical rates of decomposition because of intramolecular C–H bond activation (Section 6.2) also were observed. These findings are best rationalized by the involvement of an equilibrium between the isomers that is more rapid than the 1:1 $\text{Cu}\text{--}\text{O}_2$ adduct formation or decomposition steps (Scheme 1). The results of a recent detailed study of the solvent and temperature dependence of the ratio of the isomers are consistent with this equilibrium, and yield thermodynamic parameters for solutions in THF of $\Delta H = 4\text{ kJ mol}^{-1}$ and $\Delta S = 25\text{ J mol}^{-1}\text{ K}^{-1}$.^[39]

Subsequent to the discovery of the peroxo/bis(μ -oxo) equilibrium in the system with $i\text{Pr}_3\text{tacn}$, evidence for similar equilibria in systems supported by other ligands has been reported.^[27, 28, 30, 33] On the basis of UV/Vis, resonance Raman,

and X-ray absorption spectroscopic data (X-ray absorption near-edge spectroscopy (XANES) and EXAFS) it was shown that oxygenation of $[(\text{MePy}2)\text{Cu}]^+$ yields a mixture of $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo- and bis(μ -oxo)dicopper isomers in solution (CH_2Cl_2) and in the solid state (ratio $\approx 4\text{:}1$).^[28] Stopped-flow kinetic data were found to be consistent with a rapid equilibrium between the isomers. In addition, a compositionally disordered X-ray crystal structure akin to the one obtained for the system comprising $i\text{Pr}_3\text{tacn}$ was obtained. Interestingly, only the peroxo core was observed (UV/Vis, Raman) for the system supported by $\text{PhCH}_2\text{CH}_2\text{Py}2$, which differs from $\text{MePy}2$ only with respect to the alkyl substituent.^[40] Kinetics data for the decay of this $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo complex suggested that isomerization to a bis(μ -oxo) core occurs prior to intramolecular C–H bond activation (see Section 6.2). Isomerization of the bis(μ -oxo)dicopper unit supported by 6- Me_2tpa to a $\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo core was implicated by the observation of reversibility in the oxygenation process.^[30] Thus, bubbling N_2 through a solution of $[(6\text{-Me}_2\text{tpa})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$ in CH_2Cl_2 at -80°C or addition of PPh_3 to a solution in acetone caused ejection of O_2 and formation of monomeric Cu^{I} species, presumably via a peroxo intermediate which was not observed. More recently, mixtures of peroxo and bis(μ -oxo) isomers were observed upon oxygenation of Cu^{I} complexes of a range of peralkylated diamine ligands $\text{R}_1^2\text{R}_2^2\text{eda}$ and $\text{R}_1^2\text{R}_2^2\text{pda}$, with equilibrium constants that were sensitive to the ligand structure, solvent, counterions, and temperature.^[33] Interestingly, and in contrast to all other cases, for the system with $\text{L} = t\text{Bu}_2\text{Me}_2\text{eda}$ in MeTHF solvent, isomer interconversion was slow relative to decomposition, and differential reactivity of the two isomers both with respect to decay and to oxidations of added substrates was observed.

Taken together, the data indicating the existence of the peroxo/bis(μ -oxo) equilibrium with a range of N-donor ligands point to the potential general significance of the isomerization process in reactions that involve the making or breaking of the dioxygen O–O bond. We note that no examples of the ($\mu\text{-}\eta^2\text{:}\eta^2$ -peroxo)diiron or -dimanganese core have been identified in synthetic complexes or in biological systems. Nonetheless, and despite theoretical arguments to the contrary,^[86] it remains conceivable that such species may be involved as intermediates in bis(μ -oxo)dimetal complex generation through an O–O bond breaking process (or the opposite) now with a precedent in copper-containing systems.

The finding of either or both isomeric cores in copper complexes with divergent ligands raises questions concerning what ligand structural features are the most important in controlling which isomer predominates. Examination of the existing data suggests some general rules: bis(μ -oxo) complex formation is favored when the supporting ligand a) is bidentate, b) has strongly σ -donating amine donors, c) is less sterically hindered (smaller N-donor ligand substituents), and/or d) has a constraining tether between donor portions (e.g., $i\text{Pr}_4\text{dtne}$). These features may be understood in an intuitive way by considering the core shapes and formal oxidation states of the copper ions in the two forms. There is a long distance ($\approx 3.5\text{ \AA}$) between Cu^{II} ions in the peroxo isomer versus a short distance ($\approx 2.8\text{ \AA}$) between more

electron deficient Cu^{III} ions in the bis(μ -oxo) form. Thus, strongly electron-donating ligands that best enable (or only allow) a short intermetal separation and a square-planar coordination geometry favorable to d^8 Cu^{III} centers tend to support bis(μ -oxo) core formation. Conversely, tridentate ligands with sterically encumbered substituents or spacers that inhibit close approach of the metal ions and/or poorer electron donors tend to favor the (μ - η^2 : η^2 -peroxo)dicopper(II,II) core. It has been suggested that another factor is the $N_{\text{eq}}\text{-Cu-N}_{\text{eq}}$ bite angle; the smaller the angle, the greater the stability of the bis(μ -oxo) form that is characterized by more acute Cu-O-Cu and correspondingly more obtuse O-Cu-O angles than the peroxo isomer.^[28] This simple angular dependence was evaluated by a theoretical analysis of $[(\text{NH}_3)_4\text{Cu}_2(\mu\text{-O})_2]^{2+}$ units and was suggested to arise from differences in the energetics of the interactions between Cu and O orbitals in the two forms.^[28]

Particularly subtle effects come into play when comparing systems that have identical donor sets. For example, oxygenation of $[(i\text{Pr}_3\text{tacd})\text{Cu}(\text{CH}_3\text{CN})]^+$ in CH_2Cl_2 , THF, or acetone yields only the peroxo core, in contrast to the aforementioned behavior of the $i\text{Pr}_3\text{tacn}$ system (both isomers accessible) that differs only with respect to the deletion of a single $-\text{CH}_2$ -group within the macrocycle.^[29] A comparative analysis of the X-ray structures of the Cu^{I} precursors supported by these two ligands, in conjunction with integrated molecular orbital/molecular mechanics calculations on the complete peroxo and bis(μ -oxo) complexes, showed that the steric clashes between the $i\text{Pr}$ groups in the bis(μ -oxo) form are enhanced for the case of the larger tacd macrocycle. These clashes ultimately result in a relative quantum mechanical destabilization of the bis(μ -oxo) core that is manifested in sole experimental observation of the other (peroxo) form. Similar steric effects were invoked to explain differences in the equilibrium constants between peroxo and bis(μ -oxo) forms with bidentate peralkylated amine ligands $\text{R}_1^1\text{R}_2^2\text{eda}$ and $\text{R}_1^1\text{R}_2^2\text{pda}$, with larger $K_{\text{eq}} = [\text{peroxo}]/[\text{bis}(\mu\text{-oxo})]$ for systems supported by ligands with the same backbone but larger substituents ($\text{Me}_2i\text{Pr}_2\text{pda} > \text{Me}_2\text{pda}$) and with larger backbones and the same substituents (e.g. $\text{Me}_2i\text{Pr}_2\text{pda} > \text{Me}_2i\text{Pr}_2\text{eda}$).^[33]

The μ - η^2 : η^2 -peroxo/bis(μ -oxo) equilibration has not been observed in diiron systems, although the possibility of such a conversion has been raised in calculations of mechanisms postulated for methane monooxygenase (MMO) catalysis to account for the formation of the Fe_2O_2 core of intermediate **Q**.^[87] The synthetic (peroxo)diiron(III,III) intermediates reported to date do not contain the μ - η^2 : η^2 -peroxo unit, but instead are of the μ -1,2-peroxo type (Scheme 3), and must retain their structural integrity at the temperatures at which they are characterized.^[12b, 18d] X-ray crystal structures of three such (peroxo)diiron(III,III) complexes are known.^[88] Subsequent decomposition by raising the temperature has usually afforded no other discernible intermediate species prior to the formation of diiron(III,III) or polyiron(III) decay products. In one example, however, a (μ -oxo)(μ -1,2-peroxo)diiron(III,III) species derived from either the reaction of O_2 with $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\mu\text{-OH})_2]^{2+}$ or H_2O_2 with $[\text{Fe}_2(\mu\text{-O})_2(6\text{-Me}_3\text{tpa})_2]^{2+}$ converted in moderate yield into a high-valent species minimally formulated as $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\text{O})_2]^{3+}$.^[51, 52]

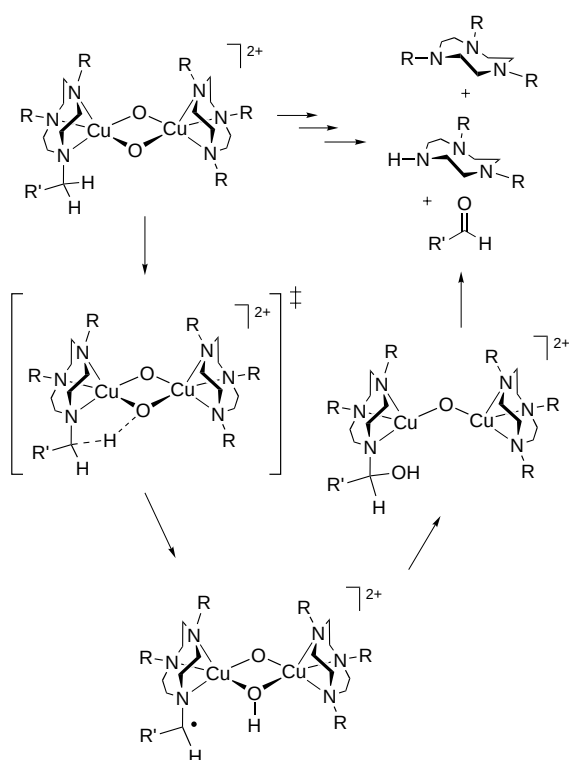
The mechanism of the conversion of the peroxo to the high-valent oxo complex is still not established.

Core isomerization of a different type has been implicated by the results of studies of the oxidation of the bis(μ -oxo)-diiron(III,III) complex supported by 6- Me_3tpa (Scheme 7).^[53] Addition of $(\text{NBu}_4)_2[\text{Ce}(\text{NO}_3)_6]$ to a solution of the complex in CH_3CN at -40°C (characterized by $E_{1/2} = 0.41$ V versus ferrocene) afforded in high yield a species that was formulated as $[(6\text{-Me}_3\text{tpa})_2\text{Fe}_2(\text{O})_2(\text{H}_2\text{O})]^{3+}$ on the basis of elemental analysis and ESI-MS data. The two oxygen atoms in the complex were found to be distinct on the basis of their different rates of exchange with isotopically labeled H_2O as revealed by resonance Raman spectroscopy. In the resonance Raman spectrum, a feature at 840 cm^{-1} was attributed to the $\nu_{\text{Fe-O}}$ of a terminal $\text{Fe}^{\text{IV}}=\text{O}$ unit that was not prone to solvent water exchange, with a small contribution from the ν_{asym} of an Fe-O-Fe unit that does exchange with water. In corroboration of this structural hypothesis, EXAFS spectra of the oxidized species show that the outer-sphere scattering between the Fe atoms characteristic for the diamond $\text{Fe}_2(\mu\text{-O})_2$ core is absent.^[89] A nearly isotropic signal with $g = 1.999$ in the EPR spectrum in conjunction with Mössbauer data indicate that the system contains a $\text{Fe}^{\text{III}}\text{Fe}^{\text{IV}}$ pair with $S = 1/2$. Taken together, the evidence supports the structure shown in Scheme 7 with an Fe^{III} center linked by an oxo bridge to a $\text{Fe}^{\text{IV}}=\text{O}$ moiety. The overall conversion from a bis(μ -oxo)diiron(III,III) complex into this product involves a coupled one-electron oxidation and bridge-to-terminal oxo migration, which suggests a flexibility of the bis(μ -oxo)diiron motif that may be of biological and catalytic significance.

6.2. Oxidations

The bis(μ -oxo)dicopper and -diiron complexes isolated so far are capable of oxidizing various organic functionalities in reactions of biological relevance, and in several cases mechanistic information is available. In general, the copper compounds are one or two-electron oxidants, whereas the iron species mainly perform one-electron oxidations.

Best studied are the ubiquitous decomposition reactions of the bis(μ -oxo)dicopper compounds, which generally proceed by attack of the C-H bonds of a supporting-ligand substituent by the oxidizing core. As illustrated for the R_3tacn system in Scheme 9, C-H bonds α to an N donor of the supporting ligand are the most common targets in these reactions. The final products are bis(μ -hydroxo)dicopper(II,II) compounds, which in several cases were shown to contain capping ligands in which an N-R group of the original ligand is replaced by an N-H moiety.^[22] The overall N-dealkylation reaction was quantified by removal of the copper ions from the product mixture and identification of the resulting organic products by NMR spectroscopic and gas chromatography (GC)/MS methods. An intramolecular pathway was shown to be operative on the basis of a) observed kinetics that uniformly are first-order in the bis(μ -oxo)dicopper complex concentration and b) a classical double-labeling experiment in which benzaldehyde product was analyzed upon allowing a mixture of



Scheme 9. Oxidative N-dealkylation reaction with postulated mechanism for an illustrative bis(μ -oxo)dicopper complex. $R = R'CH_2$, where $R' =$ alkyl and or aryl groups (see Table 5 for kinetic data).

$[(Bn_3tacn)_2Cu_2(^{16}O)_2]^{2+}$ and $[(Bn'_3tacn)_2Cu_2(^{18}O)_2]^{2+}$ ($Bn' = 4$ -*tert*-butylbenzyl) to decompose.^[90] Comparison of activation parameters (Table 5) reveals a general similarity across an array of systems, with negative $\Delta S^\ddagger$ values consistent with an ordered transition state. Importantly, large H/D kinetic isotope effects (KIEs) were uncovered that indicate C–H(D) bond scission in the rate-determining step. Indeed, the magnitude of these KIE values and their temperature dependencies implicate a tunneling contribution akin to that seen in several biological oxidations.^[91, 92] Finally, a plot of the rate constants for the series of complexes supported by $(X-Bn)_3tacn$ ($X = MeO, Me, tBu, H, CO_2Me$, and CF_3) versus σ^+ values yielded $\rho = -0.4$,^[93] a small negative value similar to those measured for H-atom abstractions by electrophilic radical reagents and heme–iron oxidants.^[94]

Taken together, the experimental evidence is consistent with a mechanism for the N-dealkylation reaction (Scheme 9) that involves rate-controlling attack of the bridging oxo unit on the α C–H bond, either by H-atom abstraction or a concerted insertion process (not shown).^[90] For the former, the resulting radical would be trapped by internal OH $\cdot$ transfer in a fast “rebound” step^[2] to yield the same intermediate carbinolamine that would result from the latter direct insertion. Fast N-dealkylation of the carbinolamine intermediate would yield the final carbonyl fragment and amine. The available experimental data does not allow distinction between the “rebound” and “direct insertion” routes, a dichotomy that parallels that which is under debate for oxidations mediated by heme and non-heme iron enzymes.^[95] It is noteworthy that recent calculations on the

Table 5. Selected activation parameters and H/D kinetic isotope effects (KIE) for decomposition reactions of $[Cu_2(\mu-O)_2]^{2+}$ complexes.

Supporting ligand	$\Delta H^\ddagger$ [kJ mol $^{-1}$] ^[a]	$\Delta S^\ddagger$ [J mol $^{-1}$ K $^{-1}$] ^[a]	H/D KIE (T [°C])	Ref.
Me ₃ tacn	53(1)	–75(12)	–	[26]
<i>i</i> Pr ₃ tacn	55(2)	–59(8)	26 (–40)	[90]
Bn ₃ tacn	54(2)	–54(8)	40 (–40)	[90]
R ₃ tacn ($n = 2$) ^[b]	60	–23	–	[31]
R ₃ tacn ($n = 3$) ^[b]	62	–39	–	[31]
Me ₃ TACD	51(2)	–100(8)	–	[29]
<i>i</i> Pr ₄ dtne	56(2)	–59(8)	40 (–40)	[23]
<i>i</i> Pr ₄ - <i>m</i> -XY ^[c]	31(1)	–151(5)	–	[24]
<i>i</i> Pr ₄ - <i>p</i> -XY ^[c]	38(2)	–108(7)	–	[24]
Et ₃ Me ₂ chd	49(1)	–105(4)	[d]	[26]
Me ₄ chd	56(1)	–100(4)	–	[26]
EtPhPy	39.1(4)	–73(2)	35 (–80)	[27]

[a] Approximate estimated error in the measured value is indicated in parenthesis. [b] R₃tacn refers to tacn ligand with aryl ether dendrimer substituents, with n = number of aromatic layers of dendron subunits. [c] Data reported for k_6 , the first of two consecutive rate constants that characterize the decay of the complexes that contain two $[Cu_2(\mu-O)_2]^{2+}$ units. [d] A KIE value of 3.0 (extrapolated to 20 °C) was measured by using ligand deuterated only at the ethyl groups to obtain a “ k_D ”. However, because involvement of C–H bond attack at the nondeuterated Me groups in this Et-deuterated ligand was not conclusively ruled out, this value may not necessarily reflect the actual KIE.

complete system supported by Bn₃tacn using an integrated molecular orbital/molecular mechanics method yielded a transition state for the rate-determining step that is consistent with H-atom abstraction (Figure 12), with reasonable agreement between the calculated and experimentally determined kinetic parameters.^[96]

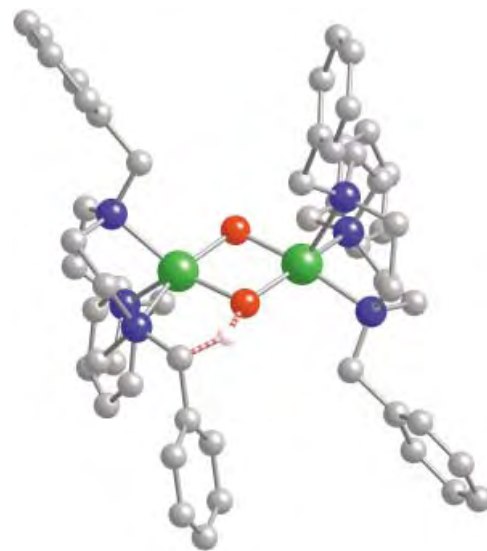
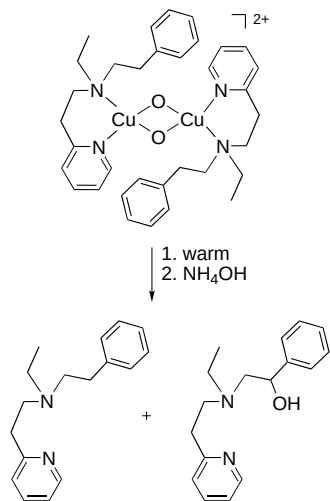


Figure 12. Structure of the transition state for the C–H bond breaking step of the N-dealkylation reaction of $[(Bn_3tacn)_2Cu_2(\mu-O)_2]^{2+}$ as determined from integrated molecular orbital/molecular mechanics calculations.^[96]

The H-atom abstraction reactivity that is implicated in the well-studied N-dealkylation pathway of the bis(μ -oxo)dicopper core also is manifested in oxidations involving other types of C–H bonds in ligand substituents and external reagents, as well as heteroatom X–H ($X = O$ or S) bonds in phenols or

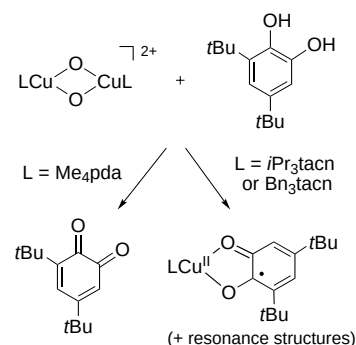
thiophenols. For example, intramolecular benzylic hydroxylation occurs upon decomposition of $[(\text{EtPhPy})_2\text{Cu}_2(\mu\text{-O})_2]^{2+}$ (Scheme 10).^[27] On the basis of kinetic studies that enabled determination of activation parameters (Table 5) and a Hammett ρ value (-1.48 , by varying the X group) similar to



Scheme 10. Intramolecular benzylic hydroxylation observed upon decomposition of the bis(μ -oxo)dicopper complex of EtPhPy.^[26]

those observed in the N-dealkylations, a mechanism directly analogous to the one postulated for the N-dealkylations was proposed. In this instance, however, the product resulting after “rebound” is a stable alcohol. A similar benzylic hydroxylation occurs for the system supported by $\text{PhCH}_2\text{CH}_2\text{Py}_2$, but a $\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo} \rightarrow \text{bis}(\mu\text{-oxo})$ conversion was proposed to be rate limiting (instead of C–H bond attack).^[40] Stereoselective hydroxylations of prochiral substituents in copper systems supported by other RPy₂ ligands also have been reported, although direct evidence for involvement of a bis(μ -oxo)dicopper intermediate was not provided.^[97]

Conversion of phenols into phenoxyl radicals is a general reaction of bis(μ -oxo)dicopper complexes, which yields coupled products or directly observable radicals depending on the substituent pattern of the phenol used. Formation of (μ -hydroxo)dicopper(II,II) species as coproduct has been observed for the Cu systems.^[20] Oxidation of catechols also is commonly observed for dicopper systems,^[34, 98] although the nature of the product isolated depends on the supporting N-donor ligand (Scheme 11). Thus, with Me_4pda complexes *ortho*-quinone formation was observed, but with R_3tacn derivatives, Cu^{II} -semiquinonato complexes were generated. Other interesting contrasts have been observed in the reactions of bis(μ -oxo)dicopper complexes of Me_4pda and R_3tacn that have been suggested to arise from differences in the accessibility of the core to external reagents.^[34] Of particular note is the unique capability of the Me_4pda complex to oxidize alcohols to aldehydes or ketones and benzylamine to benzonitrile. Binding of substrate to the Cu^{III} center(s) in this complex as a first step is implicated from preliminary

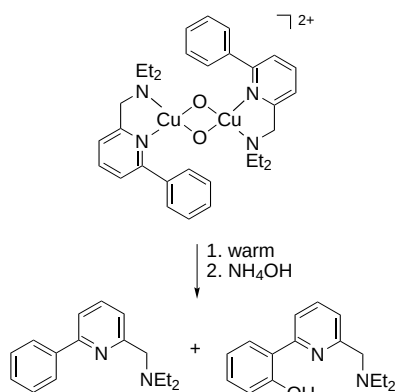


Scheme 11. Differences in reactivity of bis(μ -oxo)dicopper complexes with catechols.^[34, 98]

mechanistic studies. Corroborating the ability of the metal centers to coordinate exogenous ligands, EXAFS results have been interpreted to suggest that a perchlorate anion bridges the core.^[34]

There are also a few instances of intermolecular H-atom abstraction by $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ complexes from weak aliphatic C–H bonds such as those of cyclohexadiene or dihydroanthracene.^[35, 36] One study involves a system with a rapid $\text{Cu}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)/\text{Cu}_2(\mu\text{-O})_2$ equilibrium, so it is not clearly established precisely which moiety is responsible for the H-atom abstraction event.^[28, 35] In another study where the $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ isomer is clearly the only one present, H-atom abstraction of 10-methyl-9,10-dihydroacridine was observed.^[36] Interestingly, the observed rate law has a second-order dependence on the concentration of the bis(μ -oxo) complex. This unusual kinetic behavior requires either a ternary transition state or conproportionation of the $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ core to form an even more highly oxidized species that is responsible for the subsequent H-atom abstraction. These examples demonstrate that some of the mechanistic intricacies with respect to H-atom abstraction by $\text{Cu}_2(\mu\text{-O})_2$ complexes remain to be unraveled.

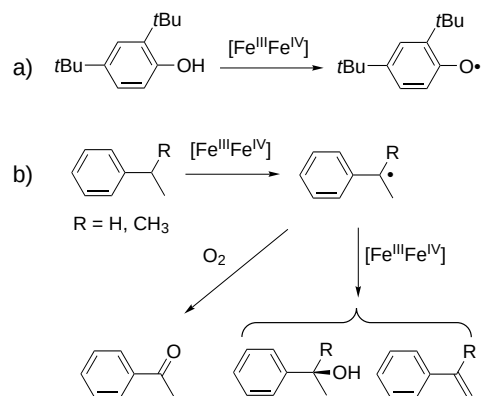
Another unresolved mechanistic issue concerns the nature of the copper/oxygen species responsible for arene hydroxylations in biological and synthetic systems.^[106] For example, while a $\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo}$ unit has been identified in tyrosinase^[34] and catechol oxidase,^[39, 99] the observation of the peroxo/bis(μ -oxo) equilibration in synthetic compounds implicates its possible occurrence in the enzyme mechanisms, and raises the possibility that a bis(μ -oxo) intermediate (yet to be observed directly) may in fact be the oxidizing species during enzymatic catalysis. Intra-^[11b, 18] and intermolecular^[100] arene hydroxylations have been observed upon decay of several (peroxo)dicopper complexes, and evidence has been presented that argues against the intermediacy of a bis(μ -oxo) isomer.^[101] Although H-atom abstraction has been the predominantly observed reaction for bis(μ -oxo)dicopper complexes, arene hydroxylation was seen when the $[\text{Cu}_2(\mu\text{-O})_2]^{2+}$ core supported by ArPyNEt_2 decomposed (Scheme 12).^[25] Rate-controlling electrophilic attack at the aromatic π system was supported by the observation of lower rates of decay for derivatives with electron withdrawing groups on the arene and the absence of a rate effect when the ring was perdeuterated. Although these results provide important



Scheme 12. Aromatic hydroxylation observed upon decomposition of the bis(μ -oxo)dicopper complex of ArPyNEt₂.^[25]

precedent for the possible involvement of the $[Cu_2(\mu-O)_2]^{2+}$ core in aromatic hydroxylation, fast pre-equilibration with a trace, but unobserved, amount of a reactive peroxo isomer cannot be ruled out. Thus, conclusive proof that the bis(μ -oxo)dicopper unit is capable of aromatic hydroxylation has yet to be obtained.

Like their dicopper(III,III) counterparts, the bis(μ -oxo)diiron(III,IV) complexes also carry out H-atom abstraction reactions. All three types of such compounds ($S = 3/2$ with tpa, $S = 1/2$ with 6-Me₃tpa, and $S = 1/2$ with ArCO₂[−]) quantitatively oxidize 2,4-di-*tert*-butylphenol to the corresponding biphenol via a phenoxyl radical intermediate (Scheme 13a).^[52, 54, 102] The two tpa complexes are reduced to (μ -oxo)diiron(III,III) complexes, so the phenol $\rightarrow$ phenoxyl radical reactions mimic the key step in the formation of the active diiron(III,III)-tyrosyl radical cofactor of ribonucleotide reductase.^[3c]



Scheme 13. Reactivity of Fe^{III}/Fe^{IV} complexes with a phenol (a)^[52, 54, 102] and hydrocarbons (b).^[102]

Oxidations more relevant to the catalytic chemistry of MMO and fatty acid desaturases have thus far been investigated only for $[(tpa)_2Fe_2(\mu-O)_2]^{3+}$.^[102] This complex reacts with hydrocarbons such as ethylbenzene and cumene to afford products that correspond to the hydroxylation of the benzylic carbon or the dehydrogenation of the α - and β -CH bonds (Scheme 13b), conversions analogous to those catalyzed by MMO and fatty acid desaturases, respectively.^[3a,b, 12] The

stoichiometry for these reactions requires the consumption of two molecules of $[(tpa)_2Fe_2(\mu-O)_2]^{3+}$ per molecule of product formed. Thus, unlike the diiron sites of the enzymes which effect two-electron oxidations of the substrate, the synthetic diiron(III,IV) complex is a one-electron oxidant. Furthermore, it can only cleave benzylic C–H bonds, not the unactivated C–H bonds that are typical of substrates for the above enzymes. Perhaps not surprisingly, the oxidizing power of the bis(μ -oxo)diiron(III,IV) core appears to be considerably less than that of the diiron(IV,IV) center generated in the MMO reaction cycle and presumed to be formed in the catalytic cycle of the fatty acid desaturases.^[3a]

Mechanistic studies of the C–H bond cleavage reactions have provided revealing insights.^[102] The kinetics of ethylbenzene oxidation at -40°C monitored by the disappearance of the green chromophore associated with $[(tpa)_2Fe_2(\mu-O)_2]^{3+}$ showed that the reaction is first order in substrate and in the dinuclear complex (second order overall) and exhibits a large KIE value of 20. This value was corroborated by measurement of the relative amounts of protio- and deuterio-products, which yielded KIE values of 22 for phenethyl alcohol formation and 28 for styrene formation. These product isotope effects show that the cleavage of the α -C–H bond is a major component of the rate-determining step for both hydroxylation and desaturation of ethylbenzene, and the larger number for styrene formation reflects the additional isotope effect (ca. 1.3) arising from the cleavage of the β -H bond of ethylbenzene. These data are consistent with a rate-determining H-atom abstraction to generate an intermediate benzylic radical, which then reacts with a second equivalent of $[(tpa)_2Fe_2(\mu-O)_2]^{3+}$ to form either the C–O bond of the alcohol product or lose a β -hydrogen en route to styrene. These second steps are relatively slow as the intermediate radical can be intercepted by O₂ to afford products derived from the decomposition of alkylperoxy radicals, for example, acetophenone. These results show that, while the isolation and characterization of a bis(μ -oxo)iron(III)iron(IV) complex represented an important step forward in establishing the viability of an Fe₂(μ -O)₂ diamond core in non-heme iron oxidation chemistry, there is still more to be accomplished in biomimetic efforts, not the least of which is the generation and study of the reactivity of a bis(μ -oxo)diiron(IV,IV) species that would correspond to MMO intermediate **Q** (see addendum).

Finally, recent studies of bis(μ -oxo)dinickel and -cobalt complexes have shown that the oxidizing capability of the M₂(μ -O)₂ unit is not limited to M = Cu and Fe.^[14–16] Decomposition of $[(Tp^{Me_3})_2M_2(\mu-O)_2]$ (M = Ni or Co) and $[(6\text{-Me}_3\text{tpa})_2Ni_2(\mu-O)_2]^{2+}$ resulted in oxidation of either a supporting ligand methyl group to its respective alcohol or N-dealkylation.^[14, 15] An H-atom abstraction pathway was implicated by a further functionalization of the ligand of the $[(6\text{-Me}_3\text{tpa})_2Ni_2(\mu-O)_2]^{2+}$ complex to yield a carboxylate group when the reaction was performed under an O₂ atmosphere. Consistent with this H-abstraction mode of reactivity, the 6-Me₃tpa-supported dinickel complex also effectively couples 2,6-di-*tert*-butylphenol. Similar reactivity with phenols was manifested by $[(EtPhPy)_2Ni_2(\mu-O)_2]^{2+}$.^[16] In addition, the decomposition of this compound in the absence of added substrate resulted in benzylic hydroxylation of the

supporting EtPhPy ligand in a process shown by mechanistic studies to involve rate-determining benzylic H-atom abstraction much like that observed for the bis(μ -oxo)dicopper analogue.^[40] In sum, the high-valent bis(μ -oxo)dimetal complexes of the later first row transition series generally display similar reactivity, most notably involving substrate oxidation by H-atom abstraction pathways.

7. Relevance to Metalloenzymes

High-valent metal centers with M_2O_2 diamond cores figure prominently in oxygen activation mechanisms currently proposed for non-heme enzymes with bimetallic active sites (Figure 13).^[3, 6, 11, 12] These mechanisms follow the well-established heme paradigm, wherein an iron(II) porphyrin center

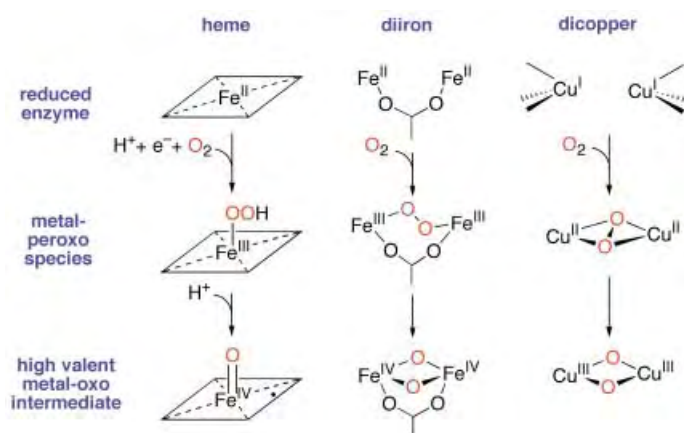


Figure 13. Unified scheme for dioxygen activation in the catalytic cycles of heme-iron and non-heme-diiron and -dicopper enzymes.

binds O_2 , picks up an electron and a proton to form a hydroperoxoiron(III) intermediate, and then undergoes O–O bond cleavage to afford an oxoiron(IV) porphyrin radical species that is primarily responsible for the oxidation of substrates.^[2] In the dinuclear context, the corresponding intermediates are a peroxo-bridged dimetal unit and a high-valent $M_2(\mu-O)_2$ species. Notably, a firm experimental basis for the notion that the latter may be involved in biological oxygen activation has been provided by the synthesis and characterization of synthetic complexes that contain the $M_2(\mu-O)_2$ core.

Although intermediates with the isomeric $[Cu_2(\mu-\eta^2:\eta^2-O_2)]^{2+}$ core^[58] have been identified for the metalloproteins hemocyanin, tyrosinase, and catechol oxidase,^[3d,f,g, 60] direct spectroscopic evidence for the metalloproteins with the isomeric $[Cu_2(\mu-O)_2]^{2+}$ core is not yet available. Nevertheless, the demonstration in some synthetic complexes of a facile equilibrium between these two cores lends support to the postulate of a $[Cu_2(\mu-O)_2]^{2+}$ species as a possible reactive intermediate. Certainly the observation of an intramolecular oxygen-atom transfer, in a synthetic $[Cu_2(\mu-O)_2]^{2+}$ complex, to a pendant arene on the ligand^[11b, 25] serves as a reasonable model for tyrosinase chemistry and makes the proposed involvement of a $Cu_2(\mu-O)_2$ core plausible.^[103]

In non-heme iron chemistry, the availability of complexes with $Fe_2(\mu-O)_2$ cores led to the design of experiments that shed light on the diiron core structure of high-valent intermediate **Q** of methane monooxygenase (MMOH-**Q**). EXAFS analysis of MMOH-**Q** showed that the diiron(IV,IV) core has an Fe–Fe distance of 2.5 Å.^[51] This rather short metal–metal distance is unique and requires the presence of at least two single-atom bridges with short metal–ligand bonds, attributes easily accommodated by the oxo bridges of an $M_2(\mu-O)_2$ core. Since the metal–metal distances in synthetic $M_2(\mu-O)_2$ complexes (Table 3) are minimally (0.2 Å) longer than that observed for MMOH-**Q**, it has been proposed that at least one other bridge is present that further constrains the metal–metal separation. This third bridge has been suggested to be a carboxylate, which is a recurring feature (E144) in all the active site structures of MMOH reported thus far.^[3h, 104] Although no carboxylate-bridged $M_2(\mu-O)_2$ complex has thus far been characterized, structural studies of synthetic bis(μ -hydroxo)diiron(III,III) complexes have shown that the Fe–Fe distance progressively shrinks from 3.11 to 2.88 Å with the addition of carboxylate bridges (Table 3, entries 14–16).^[56, 57, 61a] The proposed $M_2(\mu-O)_2(\mu-1,3-O_2CR)_n$ ($n = 1$ or 2) core formulation also has been supported by DFT calculations.^[105]

Our understanding of the nature of high-valent intermediate **X** of the diiron ribonucleotide reductase, the species responsible for the formation of the catalytically essential tyrosyl radical, has also been enhanced by the synthesis and characterization of the Fe_2O_2 complexes. This intermediate was described initially as a diiron(III,III) unit coupled to a ligand radical,^[106] but was better formulated later as an iron(III)iron(IV) complex.^[107] This reformulation coincided with the availability of the iron(III)iron(IV) complex $[(6\text{-Metpa})_2Fe_2(O)_2]^{3+}$,^[50] which exhibited similar EPR and Mössbauer properties and supported the reinterpretation of the spectroscopic data. EXAFS analysis of the iron(III)iron(IV) core of intermediate **X** revealed an Fe–Fe distance as short as that for MMOH-**Q**,^[108] consistent with the presence of an $Fe_2(\mu-O)_2$ core. However, ^{17}O electron nuclear double resonance (ENDOR) studies indicated a different structure comprising only one oxo bridge and a terminal hydroxide,^[109] which may derive from a ring-opening core isomerization similar to that established for $[(6\text{-Me}_3\text{tpa})_2Fe_2(O)_2]^{3+}$.^[53] To rationalize the short Fe–Fe distance, it is thought that an additional single-atom bridge from another ligand is present. The most plausible formulation consistent with the accumulated data is an $[Fe_2(\mu-O)(\mu-1,1-O_2CR)(\mu-1,3-O_2CR)]^{3+}$ core.

Lastly, $Mn_2(\mu-O)_2$ cores are almost certainly components of the tetramanganese cluster involved in the conversion of water into O_2 in the oxygen-evolving complex of photosystem II, as indicated by the presence of Mn–Mn distances of 2.7 Å in the various EXAFS analyses of this system.^[66] The fact that a $M_2(\mu-\eta^2:\eta^2-O_2)/M_2(\mu-O)_2$ core isomerization can occur in copper chemistry has led to the speculation that such a process may serve as the initial step towards oxygen evolution. Although quite attractive, this intriguing mechanism remains to be demonstrated for synthetic manganese complexes and for the biological entity.

In summary, we have surveyed the range of iron and copper chemistry that provides access to novel high-valent complexes with $M_2(\mu-O)_2$ cores. Although they have different electronic structures, the cores are generally structurally analogous and have in common a high degree of covalency in their metal–oxo bonding. In addition, the cores have remarkably similar Raman and EXAFS signatures, which have served as useful spectroscopic probes. They also exhibit analogous reactivity, particularly with respect to their capability to abstract hydrogen atoms from substrates. Some copper complexes have the thus far unique property of undergoing a rapid core isomerization that reversibly forms an O–O bond between the oxo bridges, while for iron a bridge-to-terminal oxo migration process has been identified. These core isomerizations illustrate how flat the oxygen activation reactivity landscape can be. The synthesis of complexes with $Fe_2(\mu-O)_2$ and $Cu_2(\mu-O)_2$ cores has opened up a new chapter in bioinorganic enzymology; it is an effort that demonstrates the important role biomimetic studies can play in advancing our understanding of metalloenzyme systems.

8. Addendum

Since submission of this manuscript, several publications have appeared that describe relevant work. Full descriptions of the properties and reactivity of several bis(μ -oxo)dicobalt(III,III) and -dinickel(III,III) complexes with tridentate N3 ligands have been reported.^[110, 111] Intermolecular oxo transfer to sulfides from a bis(μ -oxo)dicopper(III,III) unit has been discovered,^[112] but the role of this core in aromatic hydroxylation by tyrosinase was questioned in a theoretical study.^[113] A new example of a neutral $Cu_2(\mu-O)_2$ complex was reported with the use of sterically hindered β -diketiminato ligands.^[114] Finally, a novel bis(μ -oxo)diiron(IV,IV) complex relevant to MMO intermediate **Q** was isolated and identified on the basis of Mössbauer, resonance Raman, and EXAFS data.^[115]

We are indebted to the students and postdoctoral associates who have contributed to the research in our laboratories and whose names are listed in the references. In addition, we thank the NIH (GM38767 to L.Q., GM47365 to W.B.T.) and the NSF (MCB9808350 to L.Q.) for financial support. Special thanks are due to Dr. John Hagadorn for his initial work on this review and M. Henson and E. I. Solomon for providing Figure 8.

Received: July 16, 2001 [A485]

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Chirality of Living Systems: A Helping Hand from Crystals and Oligopeptides

Pedro Cintas*

Dedicated to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless

Abstract: Left–right asymmetry is ubiquitous in nature. Recent studies reveal changes in the energy and growth rate of crystal surfaces to which D or L amino acids bind, with the binding itself being dictated by stereochemical matching. Likewise, oligomerization of amino acids appears to be a chiroselective process that enables the propagation of sequences with defined handedness.^[**] These results, along with related findings on symmetry breaking and further amplification of asymmetry at a supramolecular level, constitute new insights into the origin of homochirality in living species.

Homochirality: The Problem in a Nutshell

Probably the most intriguing and challenging scientific questions are the origin of life on Earth and the origin of homochirality. From our modest terrestrial perspective, the former appears to be of prime importance though the universal handedness of matter—its left–right asymmetry at the level of elementary particles—and the cosmic preference for matter over antimatter constitute more ambitious and fascinating aspects of our observable universe.^[1, 2] The search for the ultimate origin of molecular asymmetry has been of interest to scientists since the second half of the 19th century. Not only Pasteur, who considered that a chiral physical force could be at the root of chiral substances produced in nature, but also other scientists recognized the intimate link between life and asymmetry. In 1898, the then President of the Chemical Section of the British Association for the Advancement of Science, F. R. Japp, pointed out: “The absolute origin of compounds of one-sided symmetry found in the living world is a mystery as profound as the origin of life itself... the

production of a single enantiomorph cannot conceivably occur through the chance play of symmetric forces.”^[3]

For decades, a direct connection between elementary asymmetry and biochirality has been assumed. This can be summarized in a rather reductionist underlying paradigm: one asymmetric particle leads to one enantiomer, then to one homochiral polymer, and hence to one asymmetric organism. Simply, we feel that life would have been much harder to explain if it were not universally chiral. In this regard, the electroweak interaction, by virtue of its inherent parity-violating asymmetry, could be invoked as the source of handedness in all living organisms, although a reliable and reproducible amplification mechanism has not yet been demonstrated.^[4]

Selection of Amino Acids on Crystals

Then, where does homochirality come from? Realizing that left-handed amino acids represent a signature of life, recent geochemical experiments suggest ways this chiral selection might have occurred. Thus, Hazen and co-workers have demonstrated the chiroselective adsorption of amino acids to calcite, CaCO_3 .^[5] This material was presumably one of the most abundant minerals in the Archaean era (3800 to 2500 million years ago), the middle period of the Precambrian time. Unlike hemihedral crystals, which are not identical to their mirror images (such as quartz, cinabar, and isomorphous sodium haloates), calcite is not chiral but forms mirror-image crystal surfaces, a feature displayed by crystals of numerous naturally occurring minerals. In the study by Hazen et al., a rhombohedral calcite crystal with enantiomeric scalenohedral faces (Figure 1) exhibited, when immersed in an aqueous solution of racemic aspartic acid, significant enantioselection. Thus, faces of the same handedness selectively adsorbed D aspartic acid, while the L enantiomer selectively adhered to mirror-related faces. Unfortunately, the enantioselective adsorption be-

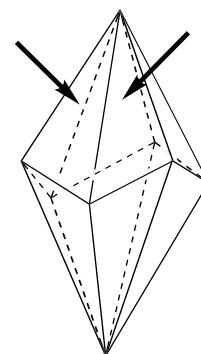


Figure 1. Typical scalenohedral crystal of calcite featuring adjacent enantiomorphous faces (arrows).

[*] Prof. Dr. P. Cintas
Departamento de Química Orgánica
Facultad de Ciencias-UEX
06071 Badajoz (Spain)
Fax: (+34)924-271-149
E-mail: pecintas@unex.es

[**] For a definition of chiroselective self-assembly, see: M. Bolli, R. Micura, A. Eschenmoser, *Chem. Biol.* **1997**, *4*, 309–320.

havior was not found for every amino acid; alanine followed a pattern similar to aspartic acid but valine and lysine were not adsorbed selectively on calcite. It is noteworthy that this selective adsorption could further be enhanced on crystals with terraced surfaces, which indicates that amino acids concentrate along steplike linear arrays.

A further reason for using calcite in these studies is related to biomineralization, where many invertebrates and plants form crystals of only one chiral habit.^[6] A well-known example is provided by the calcium oxalate crystals of tobacco and tomato leaves, which possess a chiral morphology that has been recently investigated in detail.^[7] Macroscopic chirality was long thought to be imprinted by macromolecules (such as proteins) bonded strongly to the constituent crystals in the shells of invertebrates. Nevertheless, how small peptides secreted by mineral-building organisms exert control over the morphology of a growing crystalline phase has been a controversial subject.

Recently, Orme and co-workers have shown with atomic force microscopy that calcite develops chiral crystal morphologies when grown in the presence of L- or D-aspartic acid. Molecular modeling was utilized to evaluate the free energy, and hence growth rates, of crystal surface steps to which the enantiomers bind. Depending on the chirality of aspartic acid, the growth rates of crystal steps and terraces changed asymmetrically and this resulted in an overall macroscopic chiral shape.^[8, 9] Thus, the helicity found in simple animals, from protozoans to mollusks, constitutes an important indirect piece of information about the existence of molecular enantioselectivity in the early stages of evolution.

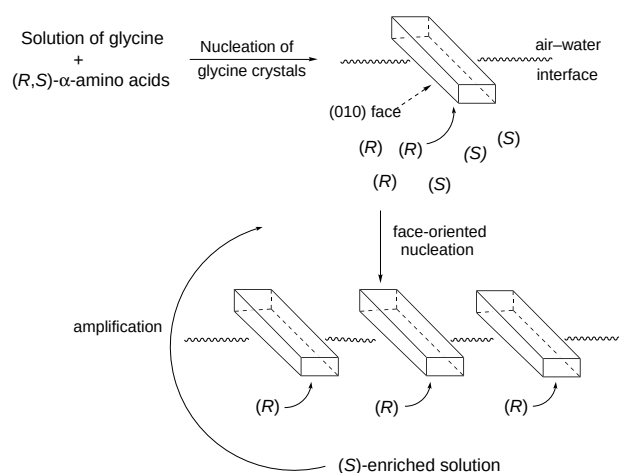
The latter results are definitely relevant, although they are based on previous studies concerning enantioselective interactions of both inorganic and organic crystals with amino acids and other biomarkers. The interactions of optically active amino acids with monoclinic gypsum (hydrated CaSO_4), another achiral mineral with enantiotopic faces, were reported by Cody and Cody,^[10] who determined that the preferential adsorption resulted in asymmetric crystal habits. Pioneering work by Leiserowitz, Lahav, and their associates revealed that impurities or additives adsorbed on growing crystal faces tend to interfere with growth along directions where there are constitutional or configurational differences between the host crystal and the impurity.^[11, 12]

Accordingly, guest molecules can selectively be incorporated into symmetry-related sites of the host lattice, thereby modifying crystal morphology. The reduction in symmetry, which can be detected by polarized light microscopy,^[13] has been observed in the mixed crystals of isomorphous salts, such as $\text{Ba}(\text{NO}_3)_2$ and $\text{Pb}(\text{NO}_3)_2$,^[14] and in the case of achiral crystals with chiral dyes.^[15] A growing crystal of di(11-bromoundecanoyl)peroxide can discriminate between almost equally sized bromine and methyl groups (their van der Waals radii are 1.9 and 2.0 Å, respectively) of an impurity in which these substituents are located at opposite termini of a symmetric long chain.^[16] The potential enantioselectivity of chiral faces has also been exploited in some asymmetric syntheses, including heterogeneous reactions^[17] and photodimerizations using mixed single crystals of reduced symme-

try, which are composed of a centrosymmetric host structure and an organic guest of similar structure and shape.^[18]

In their review on optically anomalous crystals,^[13] Kahr and McBride pointed out (on page 3): "It is easy to imagine that enantiomorphous lattice sites should be differently populated by a resolved chiral impurity, since the two kinds of defects must have different energies." The discrimination arises from the fact that most real crystals are out of equilibrium and their structural features are governed by growth kinetics rather than by thermodynamics. In this respect, one should allude to chirally autocatalytic reactions, which follow the models proposed by Frank and Calvin.^[19] Each enantiomer of the chiral product, which catalyzes the generation of further product molecules of the same configuration, is formed either from achiral reactants or from racemic reactants in a rapid equilibrium between their enantiomers. A random excess of one enantiomer in a nonchiral environment may appear due to local fluctuations or inhomogeneities, which can grow rapidly and thereby result in large enantiomeric excesses (*ees*).^[20, 21]

Scheme 1 highlights the autocatalytic crystallization of a system of glycine/ α -amino acids, which leads to the spontaneous separation of amino acids.^[22] Thus, one enantiomer from the racemic mixture may be occluded within the

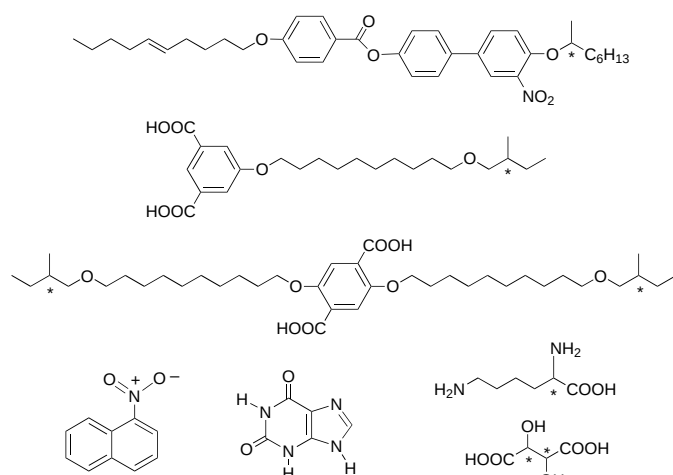


Scheme 1. Chirality amplification by oriented nucleation of centrosymmetric glycine crystals and chiroselective adsorption of α -amino acids.

centrosymmetric crystals of glycine grown at the air/water interface, whereas the other one remains in solution. Experiments with several chiral α -amino acids reveal that the (R)-enantiomers are adsorbed at the (010) face of glycine crystals and the (S)-enantiomers at the enantiomorphic face. If, by chance, one single glycine crystal exposes the (010) face toward the solution, the chiroselective occlusion of the (R)-amino acids will cause a small excess of their (S)-mirror images in solution. Such an imbalance may be able to induce a further crystal to orient with its (010) face to the solution. Repetition of this sequential nucleation/adsorption process will thus result in a solution enriched with (S)-amino acids. Furthermore, these experiments suggest feasible routes to the separation of enantiomers on two-dimensional crystallites and the formation of chiral monolayers.^[23]

Asymmetric Adsorption

It should also be noted that asymmetric morphologies can be induced upon adsorption on surfaces other than minerals, such as on carbon^[24] and metal surfaces.^[25–27] The formation of chiral kink sites as a result of the chirality induced by the adsorbed molecule in the achiral surface can be visualized by scanning tunneling microscopy (STM), which has become a useful tool for this purpose.^[28] This concept dates back to the early 1980s when Stewart and Arnett suggested that reduced dimensions should enhance chiral discrimination between mirror-image stereoisomers.^[29] Thus, while the formation of conglomerates like the ones Pasteur had identified is a rather rare phenomenon in three-dimensional space, enantiomorphic structures are often generated in two-dimensional space. There are numerous examples of this sort of mirror-symmetry breaking including the formation of Langmuir films of achiral or chiral amphiphiles containing one or more stereogenic centers, as well as discrete molecules that form achiral, racemic, or chiral domains like those depicted in Scheme 2.

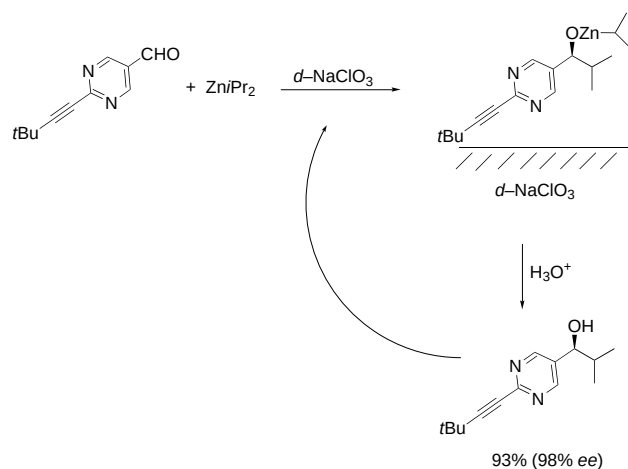


Scheme 2. Some examples of achiral and chiral molecules that produce 2D chiral domains observable by STM; see refs. [24–27].

The importance of these experiments lies in the fact that spontaneous resolution of racemates in two dimensions can be achieved, thereby mimicking the classical (Pasteur-style) separation of enantiomorphic crystals in three dimensions. In many cases, both the pure enantiomers and the racemate produce identical unit cells in monolayers. The latter strongly suggests that the racemate forms a two-dimensional conglomerate of enantiomorphic monolayer crystals upon adsorption. There are, however, exceptions in which the racemic compound does not undergo spontaneous resolution under similar experimental conditions.^[30] In addition, a major concern is also related to the formation of heterogeneous enantioselective catalysts generated by adsorbing chiral molecules onto catalytically active surfaces. STM images of the covered surface often reveal the formation of molecular clusters of varied size and oriented growth, which destroy the existing symmetry patterns of the underlying metal surface. Thus, mechanisms of enantioselective catalysis may be

rationalized in terms of adsorption on metal terraces generated by nanosized chiral aggregates, which forces a preferential orientation of the reactant molecule.^[26c]

Chiral minerals, quartz being the archetypal model, capable of existing as dextro- and levorotatory enantiomorphic forms have also been considered to have played an important role in the development of optical activity on Earth. The first reports on successful enantioselective adsorption of amino acids on optically active quartz were reported by Bonner et al. in the mid-1970s, although the *ees* were rather modest (for example D-alanine is selectively adsorbed on *d*-quartz with 20 % *ee*).^[31] In addition, a statistical analysis reveals that *d*- and *l*-quartz are equally distributed worldwide.^[32] Within this context, it is worth mentioning the intriguing results reported by Soai and his group, who obtained very large *ees* (up to 97 %) in the asymmetric addition of dialkylzincs to pyrimidinecarbaldehydes mediated by *d*- or *l*-quartz.^[33] Similarly, dextro- and levorotatory crystals of sodium chlorate were utilized in the same asymmetric addition reaction to afford the corresponding chiral pyrimidyl alcohols as (*S*) and (*R*) products, respectively, in 97–98 % *ee*.^[34] Although further studies are required, these results should most likely be attributed to diastereomeric interactions between the intermediate chiral zinc alkoxide, generated by an autocatalytic reaction, and the enantiomorphous crystal (Scheme 3). The autocatalytic cycle is most likely responsible for amplification rather than an enantioselective adsorption of chiral products on the crystal surface.



Scheme 3. Autocatalytic amplification of the formation of (*S*) pyrimidinyl alcohols in the presence of dextrorotatory NaClO₃ crystals.

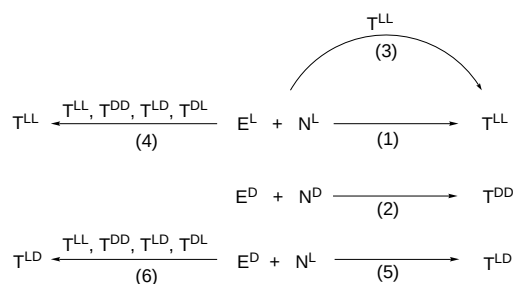
Kondepudi and co-workers demonstrated that nucleation of chiral crystals can become an autocatalytic process if the crystallization is done under continuous stirring.^[35] The amplification is due to a nonlinear effect called secondary nucleation, which is still poorly understood. During the crystallization, one mother crystal, either *d*- or *l*-, begins to produce a large number of “daughter” (secondary) crystals whose handedness thus depends on the handedness of the mother crystal (overall, there is a remarkable similarity to the above-mentioned selective orientation of enantiomorphic faces in glycine crystals). This autocatalysis exhibits a stochastic behavior, and in each crystallization almost all of

the crystals are levo- or dextrorotatory, but whether the crystals in a particular experiment will all be levo- or dextrorotatory is unpredictable. In fact, the formation of highly enantioenriched environments by stochastic sorting of conglomerate crystals has recently been proposed as a potential mechanism for the generation of prebiotic chirality.^[36]

Within the geochemical hypotheses, prebiotic models based on the catalytic and self-replicating properties of clay minerals have been proposed since the late 1940s.^[37] What about their enantiodifferentiating properties? It has been reported that L amino acids and D-glucose are adsorbed almost eight times more strongly by a naturally occurring clay mineral than their enantiomers.^[38] However, it is unclear whether a clay mineral can be considered chiral or achiral in its crystal structure. For example, there is no stereoselectivity when a racemic mixture of $[\text{Fe}(\text{phen})_3]^{2+}$ is added to a colloiddally dispersed clay suspension, as both Δ - and Λ -enantiomers are adsorbed almost quantitatively and occupy two cation-exchange sites per molecule. Nevertheless, the optical resolution of a racemic mixture through forming a diastereomeric interaction on a clay surface is feasible. In this method, an ion-exchange adsorbate of a clay and an optically active metal compound is used as a resolving agent, as one enantiomer of the racemate will be removed from a solution through being adsorbed on such a clay–chelate aggregate. Numerous substances, for example chiral octahedral complexes, 1,1-binaphthyl derivatives, and chiral sulfoxides, have been resolved by this protocol.^[39]

Formation of Homochiral Oligopeptides

The open question, however, related to the origin of homochirality on Earth is how amino acids of low enantiomeric excess were converted into homochiral oligopeptides. This fascinating question has repeatedly been addressed during the last decade.^[40] In a recent study, Ghadiri et al. suggest that peptides consisting exclusively of D or L amino acids will only replicate on templates of the same handedness.^[41, 42] The resulting copy can then serve as the template for the subsequent chiroselective synthesis. To illustrate this point, these authors have carried out template-directed condensations of a pair of electrophilic (E) and nucleophilic (N) peptides. Each pair is composed of entirely single-handed amino acids, either L (E^L and N^L) or their D counterparts (E^D and N^D). Obviously, condensations of these substrates can yield up to four templates (T), either homochiral (T^{LL} and T^{DD}) or heterochiral (T^{LD} and T^{DL}). Starting from a racemic mixture of electrophilic and nucleophilic peptides, homochiral sequences are preferentially generated. Moreover, T^{LL} autocatalytically accelerates its own production in mixtures containing N^L and E^L fragments, whereas individual addition of T^{DD} , T^{DL} , or T^{LD} to this reaction mixture had no significant influence on the reaction rate. The reaction between E^L and N^L in the presence of equimolar amounts of the four homo- and heterochiral templates exhibits a similar rate to that of the process containing T^{LL} only. In independent experiments it was shown that the formation of the heterochiral template T^{LD} remains unaffected by the presence or absence of all the other templates (Scheme 4).



Scheme 4. Chiroselective formation of homochiral templates. Pathways (3) and (4), and (5) and (6) have similar rates of product formation; see ref. [41].

Clearly, only the homochiral templates act as chiroselective autocatalysts, while the competing heterochiral fragments are formed by slower uncatalyzed reactions. Even a single heterochiral mutation can stop the self-replication of the homochiral sequences. One could therefore deduce that homochirality would ultimately emerge from a random mixture of homo- and heterochiral substrates, and it would also be possible to suggest that homochirality took place before the appearance of the genetic code.^[41b]

It should also be noted that only homochiral oligopeptides appear to form truly helical structures, as demonstrated previously in the case of oligonucleotides.^[43, 44] This is supported by the results of a recent study that showed that inclusion of D amino acids within an oligopeptide composed of L amino acids disrupts the perfect helical arrangement of the latter, presumably due to steric effects of side chains.^[45]

A further work on the chiroselective assembly of amino acids has been reported by Cooks et al.^[46] The key finding is that serine, an essential amino acid whose both enantiomers are biologically active, is mainly detected in the form of eight-membered clusters when subjected to electrospray ionization (ESI). The large relative abundance of $[(\text{Ser})_8\text{H}]^+$ indicates its great stability over other protonated serine clusters $[(\text{Ser})_n\text{H}]^+$. Moreover, this clustering process is chiroselective and thus, the octamer is readily formed from enantiopure samples, either D- or L-serine, but it was not appreciably observed from racemic serine. It is also possible to incorporate more than one type of amino acid, provided that all of the amino acids have the same handedness. Octamers composed of six D-serine molecules and two D-homoserine residues still maintain their structure and stability, as revealed by further computational studies.

A stable hexamer was also observed for cysteine, while threonine, (S)-2-aminobutanoic acid, and (R)-2-amino-1-propanol showed only dimeric forms in their ESI mass spectra. Although conclusions based on this work may be premature, it is now possible to discuss symmetry breakage at the supramolecular level of clusters,^[47] which could have implications for the evolution of homochirality of amino acids in living organisms. In a similar way to homochiral oligopeptides, the noncovalent assembly of serine molecules adopts a chirality that is dependent on that of the monomeric amino acid.

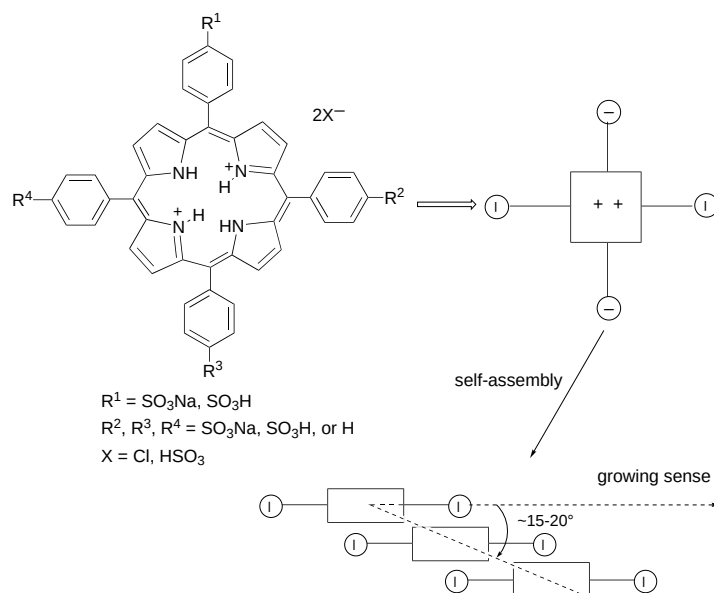
Supramolecular chirogenesis

One could imagine that mirror-symmetry breaking may be manifested on supramolecular structures, such that chiral recognition and amplification may occur at this stage. In other words, it is not essential to have chiral building blocks to observe chirality at the macroscopic level.^[48] This process, that can be called supramolecular chirogenesis, offers new insights into chirality transfer mechanisms. Nevertheless, both the control of self-assembly and the resulting stereochemical bias are not trivial issues, as chiral aggregates are often composed of left- and right-handed motifs or exhibit a poor stereo-discrimination. A notable exception may be the recently discovered chiroptical rhythmicity—the first example of a chirally oscillating reaction.^[49] Here, the sense of chirality of the macromolecular system, based on an amphiphilic rigid-rod molecule encapsulated within a hydrophobic host bilayer, flips rhythmically when a chiral ligand (*L*-histidine, but not the *D* enantiomer) is added.

The last, yet thought-provoking, example to be mentioned comes from Ribó et al., who found that homoassociation of achiral diprotonated porphyrins leads to spontaneous mirror-symmetry breaking.^[50, 51] The most salient feature of this process is that the sense of chirality of such aggregates can be selected by vortex motion. The latter is achieved by stirring in a rotary evaporator and chirality selection, detected by CD spectroscopy, is largely dependent on the rotation direction with a probability for always the same relation between rotation direction and sense of chirality close to 85%. These authors chose diprotonated *meso*-sulfonatophenyl-substituted porphyrins because such zwitterionic structures, containing both positively charged porphyrin nuclei and negatively charged ends, may self-assemble through electrostatic and hydrogen bonding interactions (Scheme 5). There is a small angle (ca. 15–20°) between the porphyrin nuclei and the growing sense of the “oligomerized” chain.

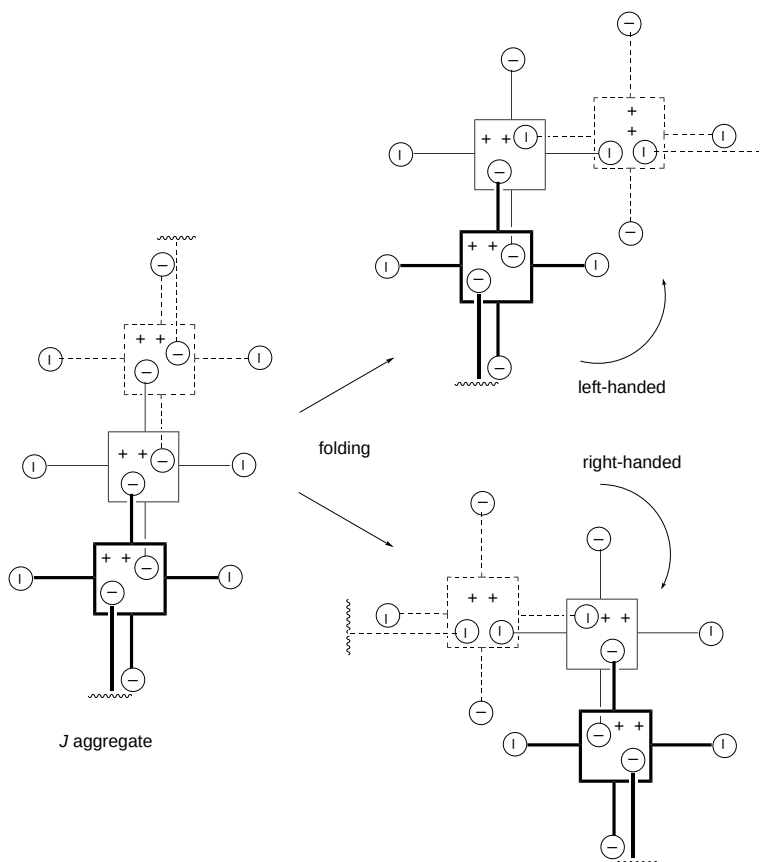
Homoassociation of these porphyrins gives rise to an edge-to-edge (*J*-aggregate) or a face-to-face (*H*-aggregate) pattern. Remarkably, a 90° fold of the unfolded, and otherwise achiral, *J*-aggregates produces nonlinear arrangements that show (*P*) or (*M*) chirality (Scheme 6). In this model, such folding constitutes the element of chiral selection at the bifurcation point of the aggregation process. The initial formation of a particular handedness will thus be biased by the externally ascribed vorticity. Still, the oligomerization process should enhance the small chiral bias obtained while inhibiting the appearance of competing enantiomers. The authors suggest that this key element of autocatalysis is provided by steric hindrance acting on the growing oligomers as they are incorporated into the folded aggregate.

It is noteworthy that Ribó et al. excluded any contribution of linear dichroism (LD) to the CD spectra of these homoassociates. The results of previous studies^[52] describing the observation of



Scheme 5. Schematic representation of the diprotonated *meso*-porphyrins employed by Ribó et al.; see refs. [50, 51].

stirring-induced CD signals in *J*-aggregates have proven to be irreproducible or attributable to LD artifacts. More recent studies, however, also claim the formation of chiral *J*-aggregates from achiral dyes without such contributions.^[53]



Scheme 6. Self-association and folding of *J* aggregates derived from zwitterionic porphyrins. Anticlockwise or clockwise vortices give rise to left-handed and right-handed chirality, respectively; see text and refs. [50, 51].

Anyway, the paper by Ribó and co-workers constitutes the first unambiguous proof of the generation of chirality under stirring as vortices, meaning fluid motion involving rotation plus translation, are a truly chiral influence.^[54] Although vortex motion is presumably involved, one might argue that, under nonequilibrium conditions, rotation would be sufficient to induce chirality. Recently it has been reported that the initial handedness of heterohelicenes may be reversed and subsequently enhanced by sonication,^[55] another class of fluid agitation yet a falsely chiral influence.^[***]

The ultimate origin of asymmetry will presumably remain uncertain, but autocatalytic cycles during crystallization and oligomerization reactions may well account for the homochirality in living organisms. The understanding of these nonlinear processes will be the next target.

Work of my group mentioned here was supported by a grant from the Spanish Ministry of Science and Technology (PB98-0997) and the Junta de Extremadura-Fondo Social Europeo (IPR00-C021).

Received: July 12, 2001

Revised: November 9, 2001 [M 1525]

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[***] True chirality is possessed by physical systems that exist in two enantiomeric states that are interconverted by space inversion but not by time reversal combined with any proper spatial rotation. Only a truly chiral influence may induce absolute asymmetric synthesis under thermodynamic equilibrium, but for reactions under kinetic control false chirality might suffice.^[54]

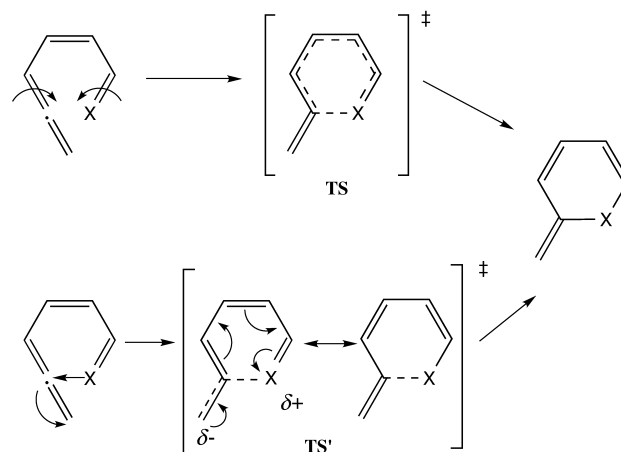
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Electrocyclization of (Z)-1,2,4,6-Heptatetraene and its Heterosubstituted Analogues: Pericyclic or Pseudopericyclic?

Jesús Rodríguez-Otero* and Enrique M. Cabaleiro-Lago

Pseudopericyclic reactions were originally defined by Lemal and co-workers as pericyclic reactions in which there is a disconnection in the cyclic array of overlapping orbitals because of the presence of orthogonal orbital systems.^[1] A pseudopericyclic reaction may, therefore, be orbital symmetry allowed by a pathway that maintains the orbital disconnections, regardless of the number of electrons involved.^[2] However, there is an ambiguity with the definition of Lemal and co-workers in that the orbital description is not unique.^[3] One of the more salient properties of this type of reaction is the presence of very low or even no energy barriers and that of planar transition states.^[4]

In a previous communication, Cossio and co-workers^[5] concluded that the cyclization of (Z)-1,2,4,6-heptatetraene (reaction C in Scheme 1) involves a pericyclic disrotatory electrocyclization via transition state **TS** (Scheme 2), whereas those of its heterosubstituted analogues (2Z)-2,4,5-hexatrien-1-imine (reaction A in Scheme 1) and (2Z)-2,4,5-hexatrienal (reaction B in Scheme 1) involve a nucleophilic addition of pseudopericyclic nature via transition state **TS'**. To our minds, however, the evidence used to support the pseudopericyclic nature of the latter two reactions is not solid enough to warrant such an assertion. In fact, at the time the communication was published, our group was in the process of studying such reactions and the results eventually obtained further



Scheme 2.

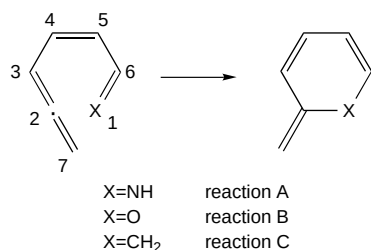
refute the hypothesis of Cossio and co-workers that the two are pseudopericyclic.

Although our density functional theory (DFT) calculations were done using a 6-31G** basis set, which was slightly smaller than that employed by Cossio and co-workers (6-31 + G*), this has no effect on the ensuing discussion, as both the geometric and energetic results were virtually identical. Thus, the bond lengths provided by the two basis sets differed by only a few thousands of an angstrom at most (see Supporting Information). Also, the activation energies provided by both B3LYP computation methods (Table 1) were very similar to each other and also very close to those obtained using Møller–Pleset computations.

Table 1. Calculated energies [kcal mol⁻¹]^[a].

		B3LYP ^[b]	B3LYP ^[c]	MP4SDTQ ^[d]
reaction A	TS	13.75	14.61	13.65
	product	-33.68	-	-32.52
reaction B	TS	14.41	14.85	14.11
	product	-17.34	-	-17.34
reaction C	TS	19.97	20.56	17.20
	product	-27.00	-	-31.37

[a] Energies relative to the most stable conformer of the reactant. The values are corrected for zero-point vibrational energies (ZPE). The ZPE were scaled by 0.9806 [ZPE(B3LYP/6-31G**)0.9806] or by 0.9608 [ZPE(MP2/6-31G**)0.9608]. [b] B3LYP/6-31G**//B3LYP/6-31G**. [c] B3LYP/6-31 + G**//B3LYP/6-31 + G*.^[5] [d] MP4SDTQ/6-31 + G**//MP2/6-31G**.



Scheme 1.

[*] Prof. Dr. J. Rodríguez-Otero, E. M. Cabaleiro-Lago
Departamento de Química Física
Facultade de Química, Universidade de Santiago
15706 Santiago de Compostela, Galicia (Spain)
Fax: (+34) 981595012
E-mail: qftjesus@usc.es



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

The first argument used by Cossio and co-workers was that “the harmonic analysis of **TSa** reveals that the nuclear motion corresponding to the imaginary frequency of its diagonalized Hessian matrix has no component associated with the rotation of the N1-H group with respect to the N1-C2 bond being formed”. This is the case not only with **TSa** but also with the transition state **TSc**, the disrotatory nature of which is unquestionable. Also, instead of focusing on this rotation, it is seemingly more simple and illustrative of the process to focus on that about the X1-C6 bond, which reflects changes in the H-X1-C6-C5 dihedral angle, for example. The animation of nuclear motion clearly shows that the dihedral angle changes in both **TSc** and **TSa**. To further support this assertion, we computed the path for the two reactions (using the intrinsic reaction coordinate (IRC) method with mass-weighted cartesian coordinates) and examined geometric changes along the reaction coordinate. Figure 1a shows the variation of the above-mentioned dihedral angle: the torsion in the H-N-C-C dihedral angle in reaction A is compared with that in the H-C-C-C dihedral angle in reaction C (by considering the appropriate proton of the methylene group in the latter case). As can be seen, the changes were very similar in both cases: the initial angle was close to 180° and a rotation was observed that increased along the reaction coordinate and peaked near the transition state. Only at the end of the reaction path did any easily interpreted differences arise; in fact, while C1 exhibits sp³ hybridization at the end of reaction C, N1 will eventually adopt sp² hybridization (with the proton in the plane) in reaction A. As a result, the dihedral angle regained a value in the region of 180°. In summary, the most salient conclusion from this graph is that the rotations in reactions A and C are similar. We conducted a natural bond orbital (NBO) analysis at different points along the reaction path to provide more conclusive support for this assertion. This calculation allows one to determine the directionality of the electron lone pair (Lp) on the N atom and hence the variation of the Lp-N1-C6-C5 dihedral angle along the reaction coordinate. Figure 1b compares such a variation with the H-C-C-C torsion angle in reaction C by focusing on the appropriate proton of the methylene group (that is, the internal proton). As can be seen, the situation was very similar; this, together with the results of Figure 1a, clearly suggests there is rotation about the N1-C6 bond in reaction A.

In regard to the rotation of exocyclic H-C7 groups with respect to the C2-C7 bond, Cossio and co-workers stated that “this rotation corresponds to the rehybridization of the C2 atom and therefore it is not associated with disrotatory motion”. At no time was this assertion supported with actual data, so we believe it constitutes no evidence; although it cannot be categorically rejected, the mere observation of the nuclear motion corresponding to the imaginary frequency of the transition state suggests no appreciable difference—as regards the rotation of these H-C7 groups—among the transition states **TSa**, **TSb**, and **TSc**. Figure 2 illustrates the similarity in the rotation of the C7-H₂ group in the three transition states.

One other argument used by Cossio and co-workers was the charge distribution in the transition states. Without question-

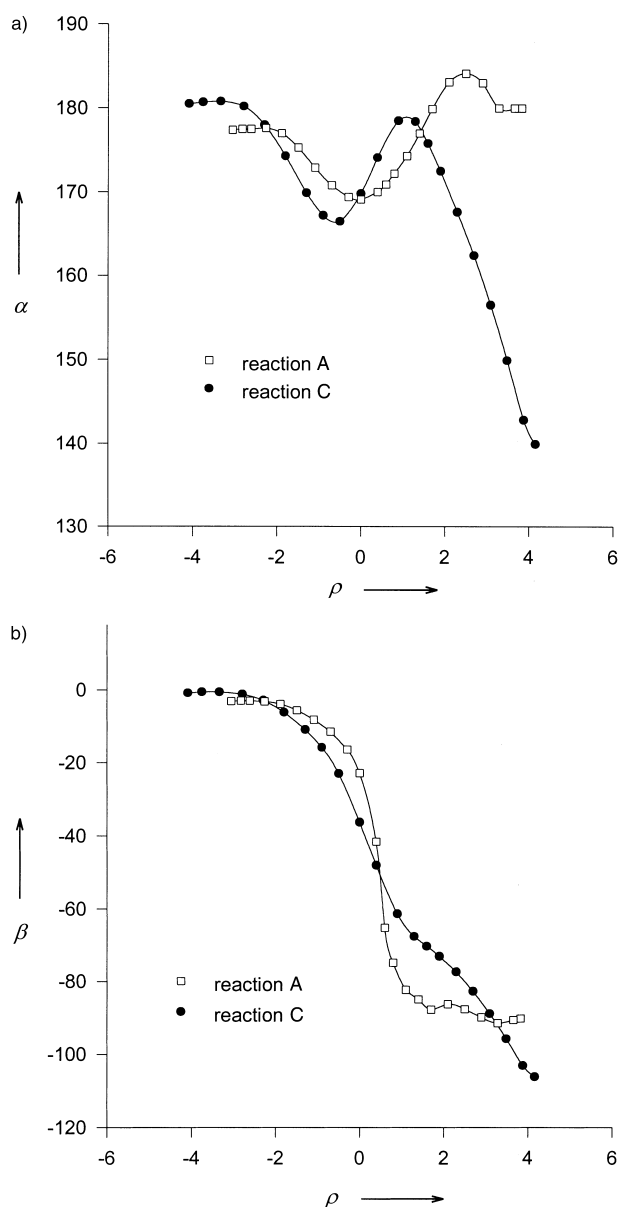


Figure 1. Modification of the H-X1-C6-C5 (a) and Lp(H)-X1-C6-C5 (b) torsion angles for reactions A and C along the reaction path ρ (amu^{1/2}·bohr). α = H-X1-C6-C5°; β = Lp(H)-X1-C6-C5°.

ing the dubious value of point charges in this type of study, the sole parameter utilized was the presence of a charge of $-0.22e$ on the C7 atom in **TSa**; this value was obtained by NBO analysis and assumed to support the hypothesis of a nucleophilic addition mechanism involving **TS'** (Scheme 2). We could not reproduce the reported charge. In fact, by using the same method, we obtained a negative charge of $-0.55e$ on C7; the divergence was not a result of using a different basis set, as the charge provided by that employed by Cossio and co-workers (6-31 + G*) was virtually the same ($-0.56e$). This divergence aside, the truly important finding was a negative charge ($-0.50e$) on C7 in **TSc** (and $-0.53e$ in **TSb**). We believe such slight differences cannot be used to discern between two potentially different reaction mechanisms.

The last argument used by Cossio and co-workers involved the aromaticity of the transition states (as determined using

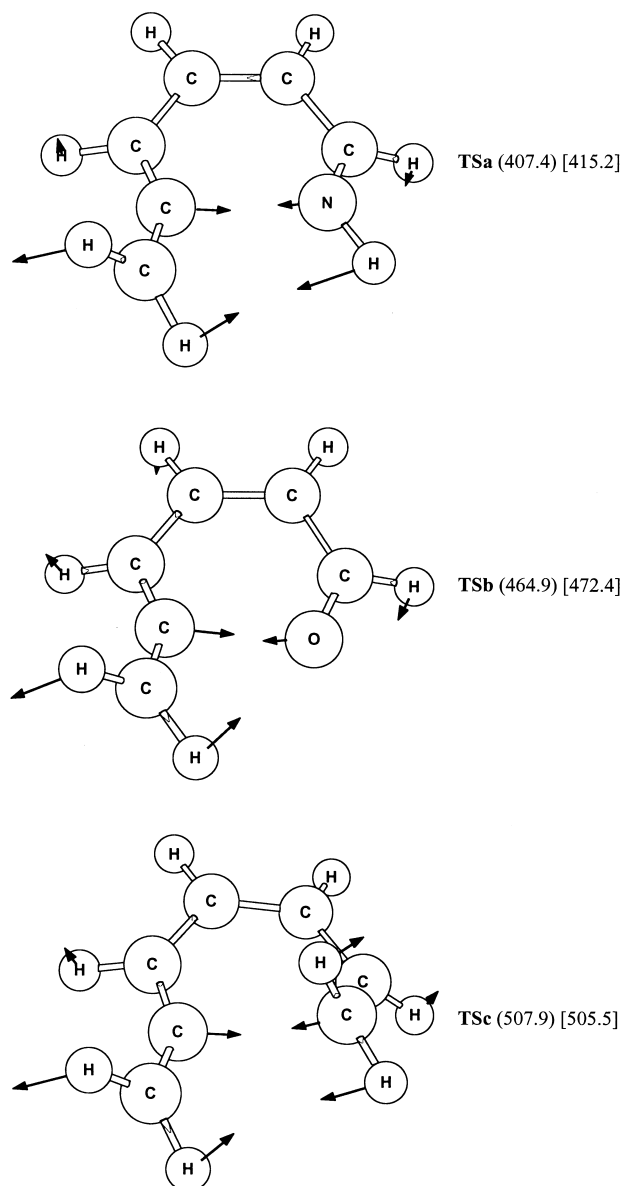


Figure 2. Transition structures and normal mode eigenvectors for the coordinate frequency. The value of the imaginary frequency (cm^{-1}) is given in each case: (B3LYP/6-31G**) [B3LYP/6-31 + G*].

the method of Schleyer et al.^[6]); in fact, pericyclic reactions are known to exhibit aromatic transition states.^[7, 8] While the maximum nucleus-independent chemical shift (NICS_{max}) is certainly much less negative for the transition states **TSa** and **TSb** than for **TSce** ($\delta = -13.64$), which indicates that the latter is more aromatic than the former two, the values for **TSa** ($\delta = -7.75$) and **TSb** ($\delta = -6.80$) also reveal a certain aromatic character; for example, benzene possesses a slightly larger NICS value ($\delta = -9.7$).^[6] In addition, recent studies have shown that aromaticity is seemingly a multidimensional property,^[9] so its quantitative determination requires the use of several criteria. One other criterion frequently employed in this context is the magnetic susceptibility anisotropy (χ_{anis}). By using the B3LYP/6-311 + G(2d,p) method in combination with IGAIM (a slight variation on the continuous set of Gauge transformations (CSGT) method), we obtained an

χ_{anis} value of -36.54 and -31.37 cgs ppm for **TSa** and **TSb**, respectively, neither of which is very different from that for pyrrole (-41.8 cgs ppm)^[10] or from that for the transition state of the Diels–Alder reaction (-43.1 cgs ppm).^[7] The corresponding value for **TSce** was -46.44 cgs ppm, which suggests that this transition state is more aromatic than **TSa** and **TSb**; however, this does not necessarily mean that these two states cannot be aromatic or that their respective reactions take place in a pseudopericyclic manner. Both the NICS and χ_{anis} values are susceptible to local effects other than aromaticity and therefore the absolute values should not be used to quantify aromaticity properly.

Now that the arguments used by Cossio and co-workers have been discussed, we introduce some additional points, which cast even more doubt on them. If reactions A and B are assumed to take place via **TS'** (Scheme 2), then, on the basis of the structure of this transition state, **TSa** and **TSb** should exhibit an appreciably lengthened C7–C2 bond as this loses (at least in part) its double bond character. However, the results contradict this assumption: the bond lengths obtained for the three transition states are similar and, paradoxically, **TSce** exhibits the longest bond (1.325 Å for **TSa**, 1.322 Å for **TSb**, and 1.328 Å for **TSce**). In addition, the Wiberg bond orders provided by the NBO analysis (namely, 1.90 for **TSa**, 1.93 for **TSb**, and 1.89 for **TSce**) suggest that the double bond remains virtually intact in the three cases. The behavior of that bond along the reaction path is very similar for the three reactions (see Supporting Information).

There is solid evidence that pseudopericyclic reactions take place via planar or nearly planar transition states.^[3] It is true that the rings in **TSa** and **TSb** are less strained than those in **TSce**. However, the structure of these rings is far from planar. In fact, if we add up the differences from 0.0° (in absolute value) of the six dihedral angles in the ring, we obtain 86.9° for **TSa**, 100.3° for **TSb**, and 129.8° for **TSce**, all at the B3LYP/6-31G** level. The B3LYP/6-31 + G* values are very similar and those provided by MP2/6-31G** suggest an even greater loss of planarity.

Let us now examine our NBO results for the transition states in greater detail. Figure 3 illustrates the directionality of

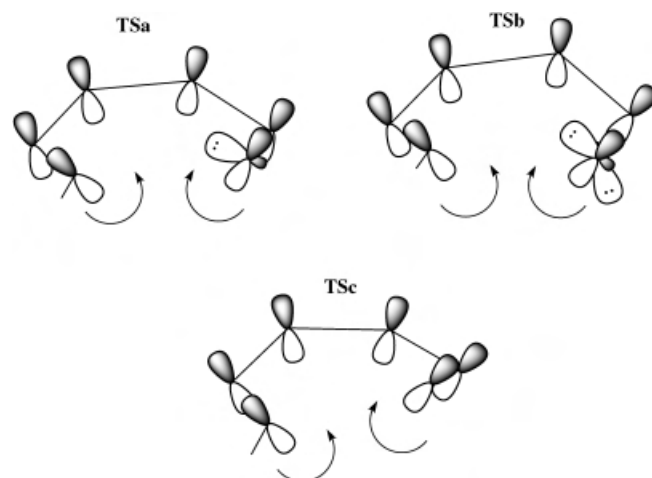


Figure 3. Schematic depiction of the directionality of the NBOs most strongly involved in the transition states **TSa**, **TSb**, and **TSce**.

the orbitals most strongly involved in the reactions. As can be seen, the position of the p orbitals (99.99% p character) are identical in **TSa**, **TSb**, and **TSc**: the X1–C6 and C2–C3 π bonds are rotated in a disrotatory manner, which is consistent with the Woodward–Hoffmann rules. Clearly, a difference exists in the involvement of the electron lone pair on the heteroatom. However, the most salient conclusion is that this lone pair does not attack C2 directly, but rather takes part in an extremely lateral overlap as the X1–C6 bond is already slightly rotated (in **TSa** the Lp–N1–C6–C5 dihedral angle is -22.9°). Thus, in **TSa** the lone pair deviates by 57° from the plane formed by the N1–C2–C3 atoms. If reaction A were pseudopericyclic, the lone pair—which would be in the N1–C2–C3 plane or very close to it—would perform a more direct attack on C2. In **TSb**, the deviation is even greater: the lone pair lies virtually normal (89°) to the O1–C2–C3 plane. Nevertheless, the role of the lone pair in **TSa** and **TSb** is very important, as judged from the energy results shown in Table 1. However, this contribution—which allows the process to take place with a reduced energy investment—does not exclude a prominent role of π orbitals in the reaction.

In conclusion, we believe that the evidence reported by Cossio and co-workers is not conclusive enough to state that reactions A and B are pseudopericyclic. Rather, the results

suggest that both are essentially pericyclic even though they are favored (or assisted) by the electron lone pair on the heteroatom. As shown in a previous paper on the electrocyclicization of hexatriene and its derivatives,^[11] the lone pair provides a reaction path with a decreased energy investment, but the essential features of the process are typical of a disrotatory electrocyclicization.

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Reply

Angel R. de Lera* and Fernando P. Cossio*

Rodríguez-Otero et al. have questioned our results on the pseudopericyclic nature of the cyclization of (2Z)-hexa-2,4,5-trienals and their Schiff bases. Since the electrocyclic nature of the all-carbon reaction reported in our paper (**6c** $\rightarrow$ **7c** transformation) has not been questioned by these authors, we will focus our discussion on the cyclization of compound **6a** of our article^[1] to form the cyclic structure **7a**, and we shall demonstrate that the analysis of Rodríguez-Otero is incorrect.

First, we must emphasize that the nature of the imaginary vibration of **TSa** corresponds to the attack of the electron lone pair of the nitrogen atom on the terminal double bond of **6a**. Animation of this imaginary frequency (for instance, by means of the MOLDEN program^[2]) clearly shows that the attack of the NH group does not involve any significant rotation around the N=C bond, although in-plane motion of the imine hydrogen atom clearly participates in the imaginary

frequency. Moreover, the geometries of the points along the intrinsic reaction coordinate (IRC) pathway at the B3LYP/6-31+G* level shows only marginal variations of the H–N=C–H dihedral angle, denoted as ω in Figure 1, motivated by small conformational variations of the cycle being formed.

Concerning the observation of Rodríguez-Otero and Cabaleiro-Lago on the magnitude of the NBO charge of the exocyclic atom, the value of about $-0.2e$ included in our article has been obtained by integration of the charges on the hydrogen atoms bonded to the exocyclic carbon atom, a common practice in computational chemistry since the charge on the isolated carbon atom has no chemical meaning. The values of about $-0.5e$ reported by these authors correspond to the isolated C7 atom and are not relevant from a chemical standpoint.

Rodríguez-Otero and Cabaleiro-Lago also report an analysis of the bond length between the C2–C7 atoms. The authors do not take into account that, according to Scheme 3 of our paper,^[1] the electronic reorganization in structure **TS'** does not necessarily imply any significant variation of the length of the C2–C7 bond. Therefore, the long discussion on this topic reported by these authors does not contribute to the elucidation of the nature of the mechanism of the cyclization.

The NBO analysis of **TSa** reported by Rodríguez-Otero and Cabaleiro-Lago is also erroneous. The most convenient tool to elucidate the nature of the reaction mechanism is to examine

[*] Prof. A. R. de Lera

Departamento de Química Orgánica
Facultade de Ciencias
Campus Lagoas-Marcosende
36200 Vigo (Spain)
Fax: (+34)86-812382
E-mail: qolera@uvigo.es

Prof. Dr. F. P. Cossio
Kimika Fakultatea, Euskal Herriko Unibertsitatea
P.K. 1072, 20080 San Sebastián-Donostia (Spain)
E-mail: qopcomof@sq.ehu.es

Bootstrap methods for assessing the performance of near-infrared pattern classification techniques

Brandye M. Smith¹ and Paul J. Gemperline^{2*}

¹Department of Chemistry, North Carolina State University, Raleigh, NC 27695, USA

²Department of Chemistry, East Carolina University, Greenville, NC 27858, USA

Received 15 June 2001; Revised 26 November 2001; Accepted 1 December 2001

Two parametric bootstrap techniques were applied to near-infrared (NIR) pattern classification models for two classes of microcrystalline cellulose, Avicel[®] PH101 and PH102, which differ only in particle size. The development of pattern classification models for similar substances is difficult, since their characteristic clusters overlap. Bootstrapping was used to enlarge small test sets for a better approximation of the overlapping area of these nearly identical substances, consequently resulting in better estimates of misclassification rates. A bootstrap that resampled the residuals, referred to as the outside model space bootstrap in this paper, and a novel bootstrap that resampled principal component scores, referred to as the inside model space bootstrap, were studied. A comparison revealed that classification rates for both bootstrap techniques were similar to the original test set classification rates. The bootstrap method developed in this study, which resampled the principal component scores, was more effective for estimating misclassification volumes than the residual-resampling method. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: bootstrap; near-infrared spectroscopy; pattern classification

1. INTRODUCTION

Large characteristic data sets are required for chemometric analysis, particularly for the development of pattern classification models. In a recent study we reported a genetic algorithm for the optimization of methods for classification of near-infrared (NIR) spectra that employed sufficiently large training sets (34–42 spectra per product); however, an insufficient number of spectra (14 per product) were left for testing and validation [1]. The spectroscopic data had been acquired off-site, thus additional measurements could not be made. When an experiment cannot be repeated, bootstrapping offers an alternative by resampling the original data to yield larger data sets [2,3]. More specifically, bootstrap resampling methods can be used in classification schemes to precisely determine classification rates and misclassification rates when undersized training or test sets are available. Small test sets that lead to sparsely populated classification volumes can be expanded by application of the bootstrap resampling method to yield more densely populated classification volumes. The increased sample density permits increased accuracy in the calculation of classification volumes and overlap integrals, which results in a better estimation of classification and misclassification rates. Two parametric bootstrap techniques were used in this research to enlarge small test sets for a better estimation of the area for

two overlapping clusters representative of two nearly identical compounds. An outside model space bootstrap method, which randomly resamples weighted residuals with replacement, and a novel inside model space bootstrap method, which randomly resamples principal component scores with replacement, were investigated.

Efron first developed the bootstrap in 1979 as a method of obtaining estimates of statistical parameters and estimates of the uncertainty in these statistical parameters [4,5]. The bootstrap can be used for estimating standard errors, confidence intervals or other statistical assessments of accuracy based upon resampling from an empirical distribution [2,3,6–11]. Bootstrapping is especially useful in cases where analytical expressions for these figures of merit are difficult to compute or impossible to derive. Furthermore, the bootstrap has been shown to yield confidence intervals with more accurate coverage probabilities relative to classical methods such as linearization and stochastic approximation [3,12]. Inexpensive and increased computing capability has led to the increased application of the bootstrap to chemical estimation problems in areas such as thermodynamics, kinetics and spectroscopy. For example, the bootstrap and a related technique known as the jackknife method have been successfully used to estimate confidence intervals for reaction rate constants [13,14]. At times when it is not possible to obtain sufficient data for testing and validation, the leave-one-out jackknife method can be used to estimate the standard errors in PCR and PLS regression coefficients [15]. In this study we report the application of the bootstrap

*Correspondence to: P. J. Gemperline, Department of Chemistry, East Carolina University, Greenville, NC 27858, USA.

resampling procedure for estimating figures of merit in pattern classification problems for chemical spectroscopy.

Unless otherwise noted, the term bootstrap usually implies a non-parametric bootstrap in which no conclusions are made with regard to the population distribution [6]. Parametric methods are used when assumptions are made concerning the population distribution [7]. A parametric bootstrap resamples from a fitted parametric model [9,10] and requires a larger data set, since the estimation of the probability function is involved [16]. The advantage of non-parametric techniques is that smaller data sets can be employed; however, the disadvantage is that when no speculations involving the population distribution are made, then the results will not have any confidence intervals [6,16].

Pattern classification techniques, as applied to chemical spectroscopy, employ multivariate statistics to classify chemical substances. Two data sets are required for this purpose: a training set and a test set. In our applications, training sets typically contain 20–40 NIR spectra of each substance in the library and include examples of all expected sources of spectral variability such as lot-to-lot differences, instrument drift, etc. During the training and library-building phase, training set objects of all substances are classified according to a statistical hypothesis test. The confidence level for the test, e.g. the probability density function, is estimated for the training object when fit to the classification model for the substance under consideration. In this study an object belongs to a class when the value of the probability density function falls inside the 95% confidence interval of the classification model for the respective class. If an object's probability density falls inside the 95% confidence interval of two or more classes, then it is identified as a member of the most similar class, e.g. the one with the smaller probability density. An object is classified as an unacceptable outlier if its probability density lies between the 95% and 99% confidence intervals of the class model. An object is classified as unacceptable if its probability density lies outside the 99% confidence interval of all classes in the library.

Once an adequate model of the expected variability in the training set is computed, test sets are analyzed to assess the performance of pattern recognition methods. Each spectrum within the test set is compared with the learned patterns and is classified accordingly. The sample is classified based upon its probability density as either belonging to a class (a member) or not belonging to a class (a non-member or an outlier) according to the rules and thresholds described previously. When classification is performed on chemically similar materials, overlapping regions may occur, resulting in sample misclassification. It is useful to estimate the degree of overlap of classification clusters; however, such estimation may be difficult when only a few samples lie in the overlap region. For example, in this study the sizes of the tests sets (14 spectra per substance) are insufficient to give accurate figures of merit for the classification methods studied. As mentioned earlier, the data supplied for this study were acquired off-site, thus additional spectra could not be recorded to increase the size of the test sets. The bootstrap method reported here is used to resample the test sets of size $n \times m$ to estimate larger test sets of size $N \times m$ that

follow the same distribution as the original test set. The procedure yields test sets with a higher point density for a better estimation of misclassification rates.

2. METHOD

Two multivariate bootstrap methods were used to model the outside and inside model spaces. The terminology 'inside model space' and 'outside model space', first adopted by Van Der Voet *et al.* [14], refers to the multidimensional space defined by a classification model that employs the k largest principal components (the inside model space) and the complementary space defined by the residuals of the k -factor principal component model (the outside model space). The outside model space bootstrapping technique randomly resamples residuals with replacement using the method of Faber [17]. The residuals are calculated by performing the singular value decomposition on the column-wise mean-corrected test set. Factors with small singular values are deleted, leaving k factors in the model. The number of factors selected is the same as the number of factors selected for the classification model [1]. The predicted test set $\hat{\mathbf{A}}$ is calculated using the truncated singular value decomposition

$$\hat{\mathbf{A}} = \mathbf{U}_k \mathbf{S}_k \mathbf{V}_k^T \quad (1)$$

The residuals $\mathbf{R}$ are found by subtracting the predicted test set $\hat{\mathbf{A}}$ from the original test set $\mathbf{A}$:

$$\mathbf{R}_k = \mathbf{A} - \hat{\mathbf{A}}_k \quad (2)$$

When bootstrap methods are used to resample residuals, it is necessary to use a weighting factor to adjust for the degrees of freedom removed by the model. For residuals that are resampled from k -factor PCA models, the residual variation is too small relative to the response variation, since the k -factor model inadvertently extracts a portion of it. In order to have an accurate simulation, the magnitude of the residuals is increased slightly by the weighing factor

$$w = \left(\frac{1}{(1 - k/n)(1 - k/m)} \right)^{1/2} \quad (3)$$

where n is the number of spectra, m is the number of digitized points per spectrum and k is the number of factors [17].

The residuals are then resampled with replacement N times, where N indicates the number of bootstrapped samples. For the resampling to be truly random, resampling with replacement must be employed for a matrix of size $n \times m$ such that the probability of a sample being resampled is always $(1/n) \times 100\%$ [15]. The residuals are presumed to be i.i.d., so the order in which residuals are resampled is unimportant [17]. In this way, duplication of the original spectra is avoided. The resampled residuals $\mathbf{R}^*$ are added back to the predicted test set $\hat{\mathbf{A}}$ to produce the bootstrap data set $\mathbf{A}^*$.

A problem arises when the residuals are added back to the original test, since the residuals $\mathbf{R}^*$ are of size $N \times m$ whereas the predicted test set is of size $n \times m$. Thus the predicted test set is repeated sequentially until n satisfies N . Once the residuals have been added to the original column-wise

mean-corrected test set, the means are added back to the test set.

The novel inside model space bootstrapping method differs from the outside model space bootstrap described above in that the scores (columns of $\mathbf{U}$) are resampled rather than the residuals. The following steps are performed to implement this unique method. First, the original test set is column-wise mean-centered and decomposed via the singular value decomposition function. The complete matrix of scores (not truncated), $\mathbf{U}$, is repeated sequentially until M , the number of bootstrap samples, is satisfied. The order of factors in each column of $\mathbf{U}$ is then randomized independently of all other columns to produce $\mathbf{U}^*$. Finally, a new matrix of spectra, $\mathbf{A}^*$, is generated from

$$\mathbf{A}^* = \mathbf{U}^* \mathbf{S} \mathbf{V}^T \quad (4)$$

This process is repeated $J = 10$ times and the resulting spectra are averaged together. In order to compensate for the effect of averaging, the averaged data were multiplied by the square root of J . Averaging is necessary to avoid repetition in the bootstrap sample. For example, when the columns of $\mathbf{U}$ are randomly selected 500 times with replacement from a small test set of 14 spectra to generate a bootstrap sample of 500 spectra, there is a significant likelihood that identical patterns in some of the scores will emerge, resulting in replicate spectra in the bootstrap sample which will in turn lead to incomplete coverage of sample distribution.

3. EXPERIMENTAL

The NIR spectra used in this study were described previously [1]. All spectra were measured from powdered materials in a standard sample cup at 4 nm intervals, covering the range from 1100 to 2500 nm. Pattern classification calculations were performed using $\log(1/\text{reflectance})$ data ratioed against a reference spectrum of a non-absorbing ceramic disk. In the original study, six different materials were considered; however, only two types of methoxylated microcrystalline cellulose (FMC Corp.), Avicel[®] PH101 and PH102, are reported here, because they were the only two materials that had overlapping clusters. These two types of microcrystalline cellulose are used as binders in pharmaceutical tableting processes and have identical chemical compositions, differing only in particle size. Training set spectra were acquired from 34 aliquots per material drawn from eight different lots each. Test set spectra were acquired from 14 aliquots per material using two lots each not used to develop training sets.

4. RESULTS AND DISCUSSION

Two classification procedures were performed to see how the classification of the bootstrapped test sets resembled that of the original test sets. Both the outside and inside model space bootstrap methods were applied to the respective test sets. Classification models including the Mahalanobis distance method and the SIMCA residual variance method were generated from the training sets using full spectra and five principal components as described in a previous paper [1]. For comparison purposes, these models were used to

classify the original test sets and the bootstrap test sets. The results are summarized in Table I. Use of the Mahalanobis distance method gave 85.7% and 85.7% correct classification for the original Avicel[®] PH101 and PH102 test set data respectively. The test sets for Avicel[®] PH101 and PH102 consisted of 14 spectra; thus the classification rates for Avicel[®] PH101 and PH102 indicated that only two samples from each test set were misclassified, which is an inadequate number of misclassified samples to accurately estimate the overlap of these two clusters. When the SIMCA residual variance analysis method was used, there was 100% correct classification of the two original test sets, which might give a false impression that the performance of the SIMCA residual variance method is superior to that of the Mahalanobis distance method in this application. As is shown later, this is not necessarily the case.

The Mahalanobis test set results were further analyzed to determine the percentage of acceptable, outlier and reject spectra for Avicel[®] PH101 and PH102 data sets. As previously noted, acceptable spectra were defined as having probability densities equal to or greater than 0.05 by Hotelling's T^2 statistic, placing these samples inside the 95% confidence interval of the training set. Outliers were defined as spectra that lie between the 95% and 99% confidence intervals of the training set, and rejects were defined as spectra that lie outside the 99% confidence interval of the training set. Comparison of the Mahalanobis test set results with the above thresholds revealed that none of the misclassified test spectra had probability densities less than 0.05, indicating that all the misclassified spectra were found to be 'acceptable' members of the wrong class. The result indicated that there were no outliers or rejects for the Avicel[®] PH101 or PH102 test sets; rather, these spectra (two from each test set) lie in overlapping regions of the classification clusters.

Avicel[®] PH101 and PH102 are chemically similar and thus have very similar NIR spectra, which in turn produces overlapping clusters. To visualize the overlapping regions, the Avicel[®] PH101 and PH102 training sets were decomposed using the singular value decomposition. The Avicel[®] PH101 test data were projected into the subspace spanned by the Avicel[®] PH102 training model, and the Avicel[®] PH102 test data were projected into the subspace spanned by the Avicel[®] PH101 training model, as shown via the following equations:

$$\mathbf{A}_{101\text{training}} - \text{mean}_{101} = \mathbf{U}_{101} \times \mathbf{S}_{101}^{-1} \times \mathbf{V}_{101}^T \quad (5)$$

$$\mathbf{A}_{102\text{training}} - \text{mean}_{102} = \mathbf{U}_{102} \times \mathbf{S}_{102}^{-1} \times \mathbf{V}_{102}^T \quad (6)$$

$$\mathbf{U}_{101\text{,tst},101} = (\mathbf{A}_{101\text{,tst}} - \text{mean}_{101}) \times \mathbf{V}_{101} \times \mathbf{S}_{101}^{-1} \quad (7)$$

$$\mathbf{U}_{102\text{,tst},101} = (\mathbf{A}_{102\text{,tst}} - \text{mean}_{101}) \times \mathbf{V}_{101} \times \mathbf{S}_{101}^{-1} \quad (8)$$

$$\mathbf{U}_{102\text{,tst},102} = (\mathbf{A}_{102\text{,tst}} - \text{mean}_{102}) \times \mathbf{V}_{102} \times \mathbf{S}_{102}^{-1} \quad (9)$$

$$\mathbf{U}_{101\text{,tst},102} = (\mathbf{A}_{101\text{,tst}} - \text{mean}_{102}) \times \mathbf{V}_{102} \times \mathbf{S}_{102}^{-1} \quad (10)$$

A scatter plot of the Avicel[®] PH101 and PH102 test data fitted to the Avicel[®] PH101 training model is shown in Figure 1.

The outside and inside model space bootstraps were

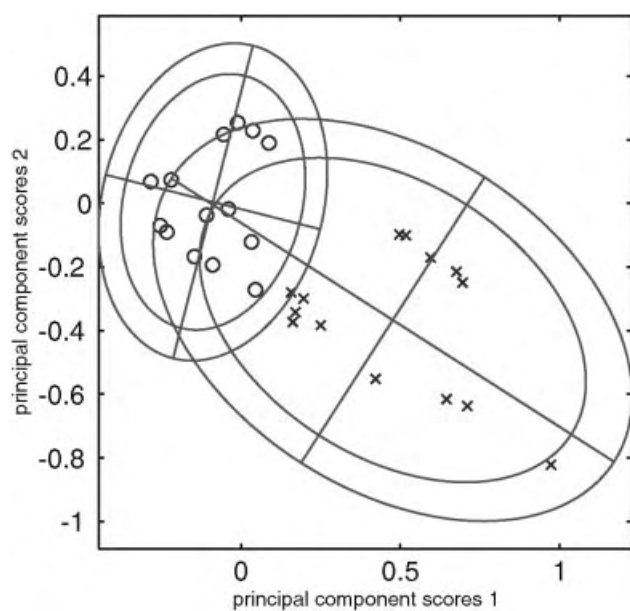


Figure 1. Plot of scores 1 and 2 of the Avicel® PH101 (crosses) and PH102 (circles) test sets fit to the Avicel® PH101 training set model.

performed on the test sets using full spectra and five factors [1]. For each test set, bootstrapped matrices of size 500×351 were constructed using the procedures previously described. The average bootstrapped matrices were classified and the corresponding confusion matrices are reported in Table I.

The Mahalanobis distance method misclassified spectra from the Avicel® PH101 and PH102 bootstrapped test sets. Without bootstrapping, the classification rate was found to be 85.7%. The inside model space bootstrapped test set had a classification rate of 91.8% for Avicel® PH101 and 86.4% for Avicel® PH102. Since the bootstrapped test set had 500 spectra, 41 Avicel® PH101 bootstrap spectra and 68 Avicel® PH102 bootstrap spectra were misclassified. The outside model space bootstrapped test set had a classification rate of 85.8% for Avicel® PH101 and 88.2% for Avicel® PH102, corresponding to 71 misclassified Avicel® PH101 bootstrap spectra and 59 misclassified Avicel® PH102 bootstrap spectra.

The SIMCA residual variance analysis method also misclassified samples from the Avicel® PH101 and PH102

inside model space bootstrapped test sets, contrary to the results obtained using the test data alone. The inside model space bootstrapped test set had a classification rate of 96.6% for Avicel® PH101 (17 misclassified bootstrap spectra) and 88.4% for Avicel® PH102 (58 misclassified bootstrap spectra). Compared with the perfect classification rates obtained for the test data alone (100% for Avicel® PH101 and PH102), these results indicate that there is overlap in the SIMCA residual variance clusters for these two materials. The bootstrap results also indicate that the SIMCA method gave lower classification errors than the Mahalanobis distance method and thus is superior to the Mahalanobis distance method in this application.

The classification rates for the bootstrapped test sets are expected to be similar to the classification rates obtained from the original test set, since the bootstrapping method is unbiased [7] and introduces no new sample information to the data. The bootstrap adds resolution in the computation of the misclassification rates, since there is a higher point density to be counted in the overlapped regions, which gives a better approximation of the volume in the overlapping clusters.

Comparing the inside model space bootstrap with the outside model space bootstrap, the outside model space bootstrap method is more conservative. This conclusion is reached owing to the consistent similarities between the outside model space bootstrap classification rates and the original test set classification rates. It is expected that the outside model bootstrap will be nearly identical to the original test set, since only the residuals are resampled.

As before, the bootstrap data were further analyzed to determine the percentage of acceptable, outlier and reject spectra for Avicel® PH101 and PH102 data sets. The probability densities for all the misclassified bootstrap spectra were greater than the 0.05; that is, once misclassified, they were found to be acceptable members of the wrong class. Regardless of which classification method or which bootstrap method was used, none of the misclassified bootstrap spectra were found to be outliers or rejects in the wrong class.

The Avicel® PH101 and PH102 bootstrap sets contain no new sample information and have the same distribution, thus the same overlapping regions, as the original test set. To validate the correctness of the bootstrap calculations described in this paper, the Avicel® PH101 bootstrapped

Table I. Confusion matrix for the Avicel® PH101 and PH102 original test sets, the outside model space bootstrapped test set and the inside model space bootstrapped test set. The actual numbers of test samples are given in parentheses

	Original test set (14×351)		Outside model space bootstrapped test set (500×351)		Inside model space bootstrapped test set (500×351)	
	Avicel® PH101	Avicel® PH102	Avicel® PH101	Avicel® PH102	Avicel® PH101	Avicel® PH102
Mahalanobis distance method						
Avicel® PH101	85.7% (12)	14.3% (2)	85.8% (429)	14.2% (71)	91.8% (459)	8.2% (41)
Avicel® PH102	14.3% (2)	85.7% (12)	11.8% (59)	88.2% (441)	13.6% (68)	86.4% (432)
Residual variance analysis method						
Avicel® PH101	100% (14)	0% (0)	100% (100)	0% (0)	96.6% (483)	3.4% (17)
Avicel® PH102	0% (0)	100% (14)	2.6% (13)	97.4% (487)	11.6% (58)	88.4% (442)

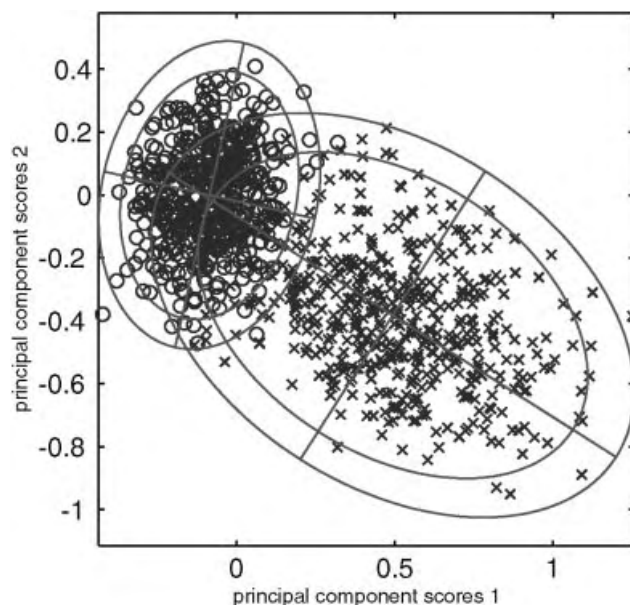


Figure 2. Plot of scores 1 and 2 of the inside model space bootstrapped Avicel® PH101 (crosses) and Avicel® PH102 (circles) data fit to the Avicel® PH101 training set model.

data were projected into the subspace spanned by the Avicel® PH102 training model, and the Avicel® PH102 bootstrapped data were projected into the subspace spanned by the Avicel® PH101 training model, in a fashion similar to the projections described in Equations (5)–(10):

$$\mathbf{A}_{101\text{training}} - \mathbf{mean}_{101} = \mathbf{U}_{101} \times \mathbf{S}_{101}^{-1} \times \mathbf{V}_{101}^T \quad (11)$$

$$\mathbf{A}_{102\text{training}} - \mathbf{mean}_{102} = \mathbf{U}_{102} \times \mathbf{S}_{102}^{-1} \times \mathbf{V}_{102}^T \quad (12)$$

$$\mathbf{U}_{101b,101} = (\mathbf{A}_{101b} - \mathbf{mean}_{101}) \times \mathbf{V}_{101} \times \mathbf{S}_{101}^{-1} \quad (13)$$

$$\mathbf{U}_{102b,101} = (\mathbf{A}_{102b} - \mathbf{mean}_{101}) \times \mathbf{V}_{101} \times \mathbf{S}_{101}^{-1} \quad (14)$$

$$\mathbf{U}_{102b,102} = (\mathbf{A}_{102b} - \mathbf{mean}_{102}) \times \mathbf{V}_{102} \times \mathbf{S}_{102}^{-1} \quad (15)$$

$$\mathbf{U}_{101b,102} = (\mathbf{A}_{101b} - \mathbf{mean}_{102}) \times \mathbf{V}_{102} \times \mathbf{S}_{102}^{-1} \quad (16)$$

Scatter plots of the resulting calculations for the inside model space bootstrap are shown in Figure 2. The shape and location of these bootstrap clusters are the same as those of the original test set clusters shown in Figure 1. Calculating and comparing the length and orientation of the major and minor axes of the 95% confidence interval ellipses shown in Figure 2 confirmed this. As expected, small differences on the order of 1% or less were observed owing to the random nature of the bootstrap resampling procedure. The overlapping regions of the Avicel® PH101 and PH102 clusters in Figure 2 can be used to visualize the degree of overlap that leads to misclassification rates characteristic of the given data sets; however, it must be recognized that the visualization is incomplete. Five principal components were used in the classification models, whereas only two principal components are shown. Additional partial separation is achieved in the space spanned by principal components 3–5, which are not illustrated in Figure 2.

Although not shown, scatter plots using data from the

outside model space bootstrapping technique (resampled residuals) do not characterize the extent of overlap as well as the inside model space bootstrapping technique. Because only the residuals are resampled in the outside model space bootstrap, the 500 bootstrap points appear nearly coincident with the positions of the original 14 samples when scatter plots are constructed using principal components 1–5. This is to be expected, since the original Avicel® PH101 and PH102 spectra, characterized by five-factor PCA models, remain largely intact in the outside model space bootstrap method. Only the residuals, characterized primarily by principal components six to n , are different from the original spectra. Thus significant scatter does not appear until plots using principle components 5 and 6 are constructed. This is the primary reason why the inside model space bootstrapping method yields a higher point density in the overlapping regions of the clusters. The higher point density seen in Figure 2 gives a better approximation of the degree of overlap of the Avicel® PH101 and PH102 clusters.

5. CONCLUSIONS

Since the test sets used in this paper were small in size, the bootstrap resampling technique was used to obtain a larger number of spectra. Outside and inside model space bootstrap methods were developed and applied to two respective test sets. The outside model space bootstrap, which resamples residuals of a k -factor principal component model, was performed on the two test sets using full spectra and five factors. The inside model bootstrap, which resamples the principal component scores, used full spectra and five principal components. For each test set, bootstrapped matrices of size 500×351 were constructed and classified.

The classification rates for the bootstrapped test sets were similar to the classification rates obtained from the original test set, since the bootstrapping method introduces no new sample information to the data. The bootstrap was effective in adding resolution in the computation of the misclassification rates, since there was a higher point density to be counted in the overlapped regions.

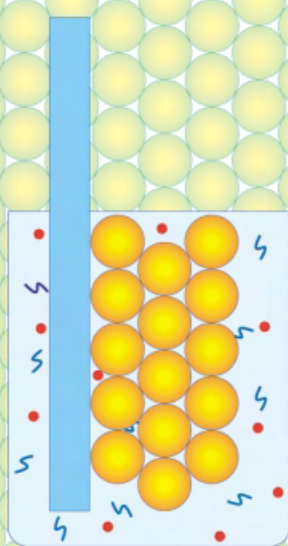
Comparing the inside model space bootstrap with the outside model space bootstrap, the outside model space bootstrap classification rates were identical to the original test set classification rates, suggesting that it is an inappropriate method for estimating figures of merit in pattern classification methods. The inside model space bootstrap was more effective at providing a higher point density, which gave a better estimate of the area in the overlapping clusters.

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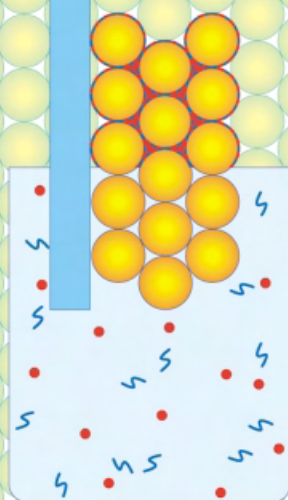
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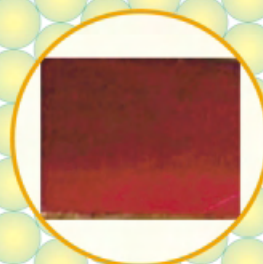
By using a dipping method metal nanoparticles were immobilized on the surface of a three-dimensionally ordered macroporous film. The circles show the film before (left) and after (right) the coating. The localized surface plasmon resonance of the nanoparticles and the stop-band of the film can be observed after immobilization. The positions of the extinction peaks depend on the surrounding medium (see diagram). For more information see the following pages.



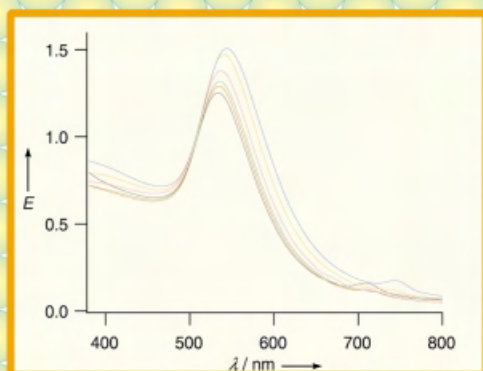
Coating



Drying



Calcination



Fabrication of a Metal-Coated Three-Dimensionally Ordered Macroporous Film and its Application as a Refractive Index Sensor**

Zhong-Ze Gu, Rumiko Horie, Shoichi Kubo, Yasuhiro Yamada, Akira Fujishima, and Osamu Sato*

Nanoparticles are of interest because of their unique optical, magnetic, and electronic properties, which are different from those of bulk materials.^[1–5] They are expected to have wide applications in optical devices and catalysis, and as chemical and biological sensors. Nanoparticles of noble metals such as gold and silver are attractive because of their so-called localized surface plasmon resonance (LSPR), which manifests itself as an absorption band when the incident photon frequency is resonant with the collective oscillation of the conduction electrons.^[6,7] The LSPR frequency of the nanoparticles is a function of their shape and of the surrounding medium. Under the isolated approximation, their relationship can be expressed by Equation (1),^[8] where κ is the absorption coefficient, N is the numerical density of the nanoparticles, ϵ_1 and ϵ_2 are the real and imaginary parts of the dielectric constants of nanoparticles, and ϵ_m is the dielectric constant of the surrounding medium. From Equation (1), the LSPR absorption depends on the dielectric constant of the surrounding medium. By exploiting this property, metal nanoparticles have been used to construct chemical and biological sensors for detecting the surrounding medium.

$$\kappa = \frac{8\pi N R^3}{27} \frac{\epsilon_m^2 \epsilon_2}{(\epsilon_1 + 2\epsilon_m)^2 + \epsilon_2^2} \quad (1)$$

Much work has been devoted to developing sensors from silver and gold nanoparticles suspended in solution.^[9,10] In some cases, it is necessary to immobilize the nanoparticles on a substrate because immobilized nanoparticles are more stable. The most common method for silver and gold nanoparticles is chemical immobilization with compounds such as alkanethiols.^[11,12] Recently, it was shown that physical immobilization can also be effective. Nanoparticles were immobilized on a substrate by evaporating a metal through a mask to give two-dimensional nanoparticle arrays^[13,14] that act as

efficient sensors for detecting the surrounding medium. Here we report a colloidal approach to immobilizing nanoparticles on a substrate by exploiting the structural properties of a three-dimensionally ordered macroporous (3DOM) film. Use of the nanoparticle-modified 3DOM film as a refractive-index sensor is demonstrated.

The fabrication of gold-coated 3DOM films is depicted in Figure 1. First, 3DOM films were fabricated on a glass substrate by vertical deposition^[15,16] of silica spheres with diameters of 195 or 300 nm in ethanol. The substrates were

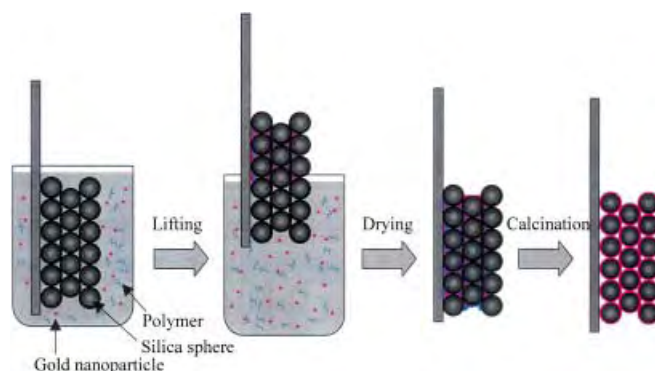


Figure 1. Outline of the fabrication of the gold-coated 3DOM film.

dried in air before use. To coat the 3DOM film, the substrate was immersed in ethanol containing gold nanoparticles with an average diameter of 10 nm. To prevent complete filling of the voids in the 3DOM films by metal nanoparticles, polymer additives were added to the solution (metal/polymer 3/1 w/w). Then the substrate was lifted out of the solution at a speed of 2 mm min⁻¹. During the lifting process, both the nanoparticles and the polymer additives infiltrated into the voids in the 3DOM film simultaneously. Then the films were dried in air and calcined at 300 °C to remove the polymer filling the voids and to immobilize the nanoparticles on the surfaces of the silica spheres.

Figure 2 shows the 3DOM film before and after gold coating. The uniform color of the films over a large area indicates that the gold was uniformly distributed, and the color after coating depends on the size of the spheres in the 3DOM film. The UV/Vis spectra of the films (Figure 3) show two peaks. The peak around 527 nm, assigned to the LSPR of gold, is in almost the same position as that of the gold colloid and indicates that the nanoparticles themselves were immobilized. After gold coating, the yellow color of a bulk gold film was only observed in the areas without the 3DOM film (at the bottom of the coated substrates in Figure 2). This indicates that the gold nanoparticles aggregate without the 3DOM film. The prevention of aggregation in the 3DOM film can be ascribed to the unique structural properties of the 3DOM film, in which the largest voids for infiltration of gold nanoparticles and polymers are only 45% of the size of the silica spheres.^[17] The other UV/Vis peak of the gold-coated 3DOM film depends on the size of silica spheres. It appears at 426 nm for 195-nm silica spheres, and at 639 nm for the 300-nm spheres. These peaks arise from the stop-band of the 3DOM, which originates from the diffraction of the three-

[*] Dr. O. Sato, Dr. Z.-Z. Gu

Kanagawa Academy of Science and Technology
KSP Building East 412, 3-2-1 Sakado, Takatsu-ku
Kawasaki-shi, Kanagawa 213-0012 (Japan)
Fax: (+81) 44-819-2070
E-mail: sato@fchem.chem.t.u-tokyo.ac.jp

R. Horie, Prof. Y. Yamada
Department of Chemistry, Faculty of Science
Science University of Tokyo
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)

S. Kubo, Prof. A. Fujishima
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo Bunkyo-ku, Tokyo 113-8565 (Japan)

[**] This work was supported in part by the Japan Society for the Promotion of Science, and the Kanagawa Prefecture Joint-Research Project for Regional Intensive, Japan Science and Technology Corporation.

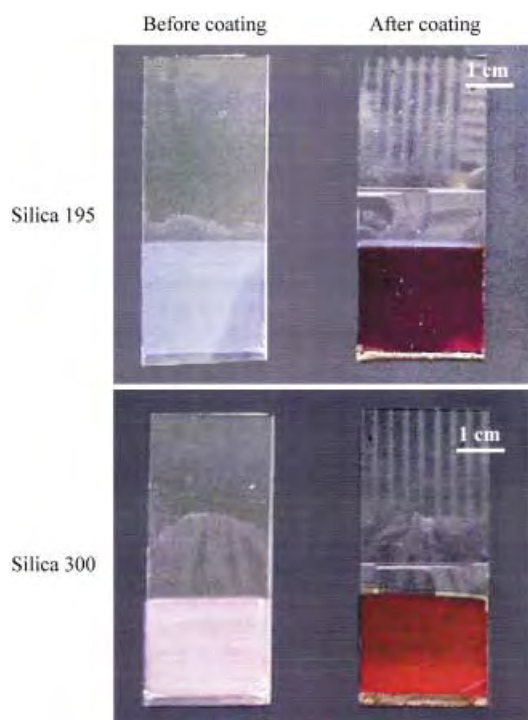


Figure 2. 3DOM films on glass substrates before and after gold coating.

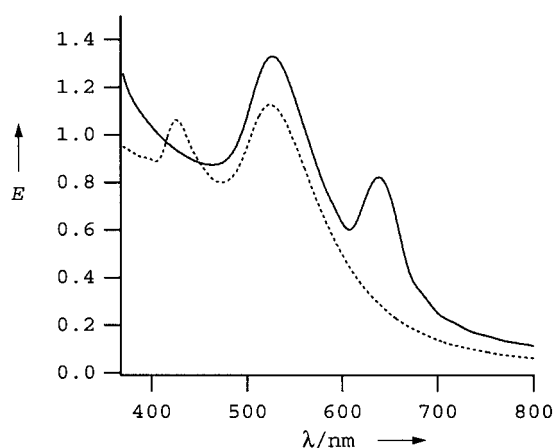


Figure 3. Transmission spectra of the gold-coated 3DOM films composed of silica spheres with a diameter of 300 (—) or 195 nm (---).

dimensionally ordered structures.^[18] This indicates that the ordered structure of the 3DOM film was maintained after gold coating. This conclusion is supported by scanning electron microscopy (SEM) images (Figure 4), which show that the hexagonally ordered structure can be observed both before and after coating.

The suitability of the gold-coated 3DOM film as a refractive index sensor was investigated by immersion in solvents with different refractive indices: methanol ($n=1.329$), ethanol ($n=1.360$), 2-propanol ($n=1.377$), THF ($n=1.407$), DMF ($n=1.431$), toluene ($n=1.496$) and 1,2-dibromoethane ($n=1.538$). The normal transmission spectra of the substrate in these solvents are shown in Figure 5. Both the LSPR peak and the 3DOM stop-band depend on the solvent. The LSPR peak shifts by 23 nm from 520 nm to 543 nm when the refractive index increases from 1 to 1.538 (Figure 6), while the stop-band

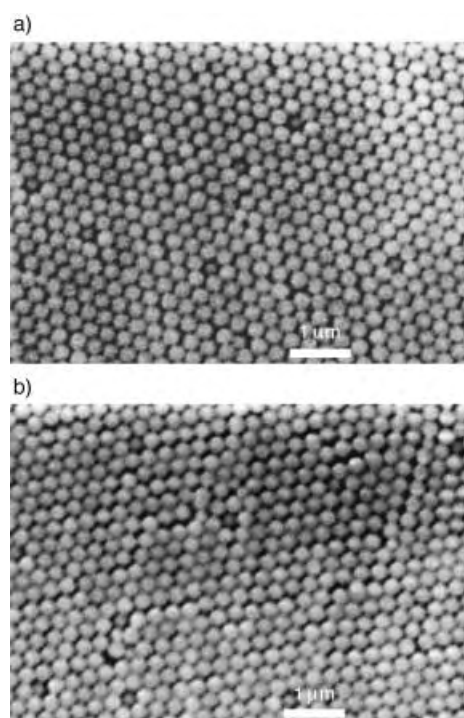


Figure 4. SEM images of the 3DOM film before (a) and after (b) gold coating. Scale bar = 1 μm .

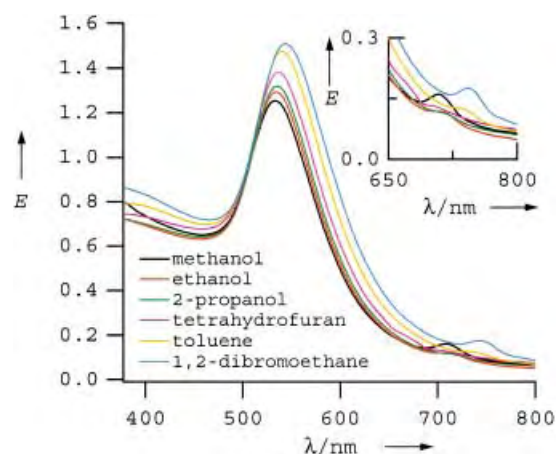


Figure 5. Spectra of the gold-coated 3DOM film composed of 300 nm silica spheres in different solvents. The inset shows an enlarged plot of the region between 650 and 800 nm to illustrate the change in the stop-band.

of opal shifted by 84 nm from 660 nm to 744 nm. Because the origins of the two peaks are completely different, their responses to changes in the surrounding medium are dissimilar. The larger shift of the stop-band (see Figure 6) compared to that of the LSPR indicates that the former is more sensitive to changes in the surrounding medium than the latter. Therefore, the stop-band is more suitable for the precise measurement of the change in refractive index of the surrounding medium. The intensity of the stop-band peak is also sensitive to the refractive index of the medium. It decreases significantly when the refractive index is near to that of silica, and disappears at around 1.45. Therefore, it is difficult to measure the refractive index of the surrounding medium in this region. On the other hand, the peak originat-

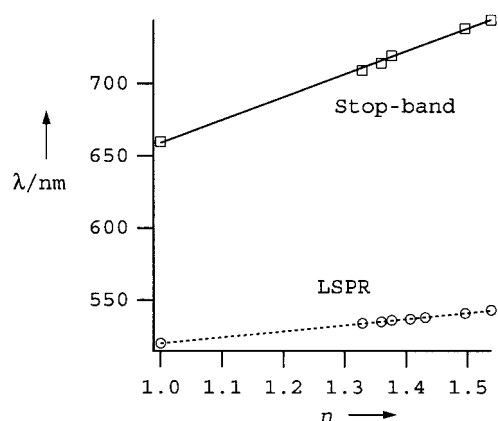


Figure 6. Dependence of the peaks originating from the LSPR (○) and the stop-band (□) on the refractive index. The dotted and solid lines were fitted by using linear functions.

ing from the LSPR can be clearly observed when the refractive index of the surrounding medium changes from 1 to 1.538. Hence, the LSPR can be used to determine any refractive index in this range. In summary, there are both merits and drawbacks to using the LSPR or stop-band peak alone to detect the surrounding medium, while a combination of the two peaks can give a more correct and precise result.

In conclusion, a high-quality metal-coated 3DOM was fabricated by a dipping method, and its application as a refractive index sensor was demonstrated. Both the LSPR and the stop-band can be used to measure the changes in the refractive index, and a combination of the two allows precise measurement of the refractive index of the surrounding medium over a wide range. Potential applications of this kind of film are as a biological sensor and as a vapor sensor. In addition, such a material may also have applications in surface-enhanced Raman scattering (SERS) and metal optical crystals.

Received: December 3, 2001 [Z18318]

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A One-Dimensional BaI₂ Chain with Five- and Six-Coordination, Formed within a Single-Walled Carbon Nanotube**

Jeremy Sloan,* Sara J. Grosvenor, Steffi Friedrichs, Angus I. Kirkland, John L. Hutchison, and Malcolm L. H. Green

Single-walled carbon nanotubes (SWNTs)^[1] are cylindrical sheets of sp² graphene carbon that, when formed by laser ablation^[2] or arc vaporization,^[3] form capillaries with diameters predominantly within the range of 1 to 2 nm. We have recently reported that one-dimensional (1D) crystals of rock-salt KI formed within these narrow capillaries exhibit a partial or total reduction in coordination.^[4,5] For example, a 1D KI crystal of 2 × 2 atomic layers formed within SWNTs 1.4 nm in diameter exhibits a total reduction from 6:6 (i.e., cation:anion) to 4:4 coordination.^[4] Similarly, a 1D KI crystal of 3 × 3 atomic layers observed within wider SWNTs (1.6 nm in diameter) exhibits three separate coordinations of 6:6, 5:5, and 4:4 along central, face, and edge -I-K-I-K- rows, respectively.^[5] Binary halides derived from layered or 3D polyhedral framework structures inserted into SWNTs form 1D polyhedral chain structures^[6] that also exhibit reduced cation and anion coordination. For example, six-coordinate

[*] Dr. J. Sloan, S. J. Grosvenor, S. Friedrichs, Prof. M. L. H. Green
Inorganic Chemistry Laboratory
University of Oxford
South Parks Road, Oxford OX13QR (UK)
Fax: (+44) 1865-272690
E-mail: jeremy.sloan@chem.ox.ac.uk
Dr. J. L. Hutchison
Department of Materials
University of Oxford
Parks Road, Oxford OX13PH (UK)
Dr. A. I. Kirkland
University of Cambridge
Department of Materials Science and Metallurgy
Pembroke Street, Cambridge CB23QZ (UK)

[**] The authors acknowledge financial support from the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 33765-AC5), the EPSRC (Grant Nos. GR/L59238 and GR/L22324) and Colebrand Ltd. Additionally, J.S. is indebted to the Royal Society for a University Research Fellowship, while S.F. is indebted to BMBF and to Fonds der Chemischen Industrie.

Cd^{2+} in CdCl_2 and nine-coordinate Tb^{3+} in TbCl_3 form five- and six-coordinate 1D zigzag polyhedral chains within SWNTs, respectively.^[7,8] While both these structures form with a reduced rearranged anion sublattice, they retain effectively the cation sublattice of the corresponding bulk halides. Here we report the first example of a 1D crystal chain derived from an alkaline earth metal halide (BaI_2) for which both sublattices are substantially different from those found in any of the published forms of the bulk halide.

BaI_2 is one of a group of dihalides that adopt the nine-coordinate $Pn\bar{m}$ cotunnite PbCl_2 structure under standard conditions^[9] but which transforms into a hexagonal $P\bar{6}2m$ form under 3 GPa pressure^[10] and a 10-coordinate post-cotunnite monoclinic $P112_1/a$ form between 5 and 15 GPa pressure.^[11] The $Pn\bar{m}$ and $P\bar{6}2m$ forms both consist of a 3D network of face-sharing distorted tricapped trigonal prisms (Figure 1a and b), the major difference being that, for the latter, the I^- coordination is more symmetrical. The highest pressure version consists of a network of tetracapped trigonal prisms (Figure 1c) and, together with the $Pn\bar{m}$ and $P\bar{6}2m$ forms, these are the only coordinations reported for Ba^{2+} within BaI_2 .

A sample of SWNTs was prepared by a catalytic arc-synthesis route^[12] and filled with BaI_2 by capillary wetting.^[13,14] The composite was examined in a 300-kV high-resolution (HR) field emission gun transmission electron microscope (FEGTEM). Lattice images showed that only 10–20% of the SWNTs contained filling, which was predominantly crystalline but also very sensitive to the electron beam, with the result that it became glassy after irradiation at a beam dosage of $5 \times 10^5 \text{ e}^- \text{ nm}^{-2} \text{ s}^{-1}$ for longer than about 20 s. Single HRTEM images were therefore obtained from the crystals in conventional imaging mode with low electron beam dosages ($2 \times 10^5 \text{ e}^- \text{ nm}^{-2} \text{ s}^{-1}$). Even under these conditions, it was not possible to use the previously described focal series restoration approach^[5,15] to image the specimen.

An image and the corresponding detail, obtained close to ideal Scherzer HRTEM focusing conditions, of a BaI_2 -filled SWNT 1.6 nm in diameter overlying two unfilled SWNTs are shown in Figure 2a and b. The microstructure of the filling material is clearly visible as a 2D array of dark spots which are lighter in intensity close to the walls of the SWNT and heavier in intensity towards its center. As the electron-scattering power of Ba ($Z=56$) is similar to that of I ($Z=53$) we assume that the dark spots correspond to

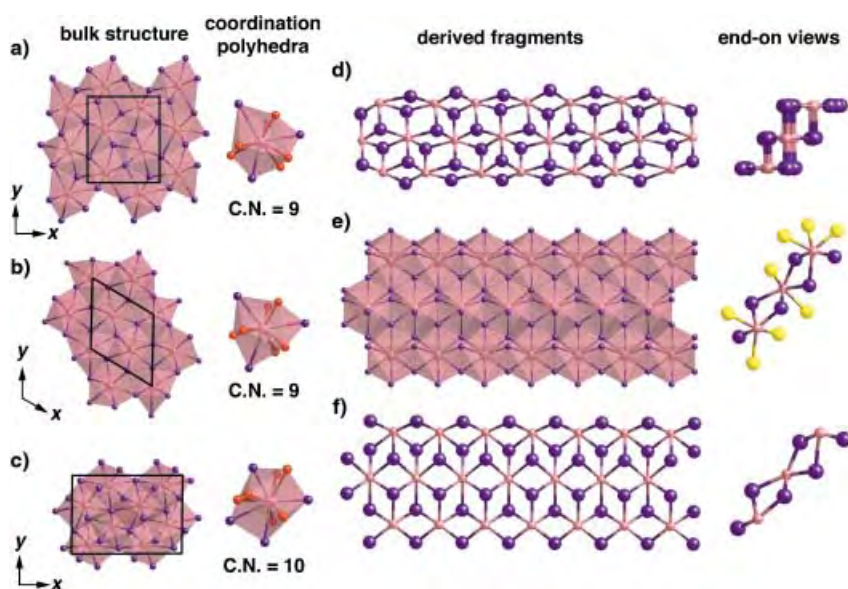


Figure 1. a) Cotunnite $Pn\bar{m}$ form of BaI_2 . b) Hexagonal $P\bar{6}2m$ modification of BaI_2 formed under 3 GPa pressure. c) 10-coordinate $P112_1/a$ form of BaI_2 formed between 5 and 15 GPa pressure. d) Staggered view and end-on representation of a 1D BaI_2 chain incorporated in a SWNT. e) Side-on and end-on views of the fragment which can be defined along z for both the $Pn\bar{m}$ and $P\bar{6}2m$ forms. The net stoichiometry of the structure can be restored to BaI_2 by removing the iodine atoms marked yellow (end-on view). f) Side-on and end-on views of reduced-coordination BaI_2 fragment. C.N. = coordination number.

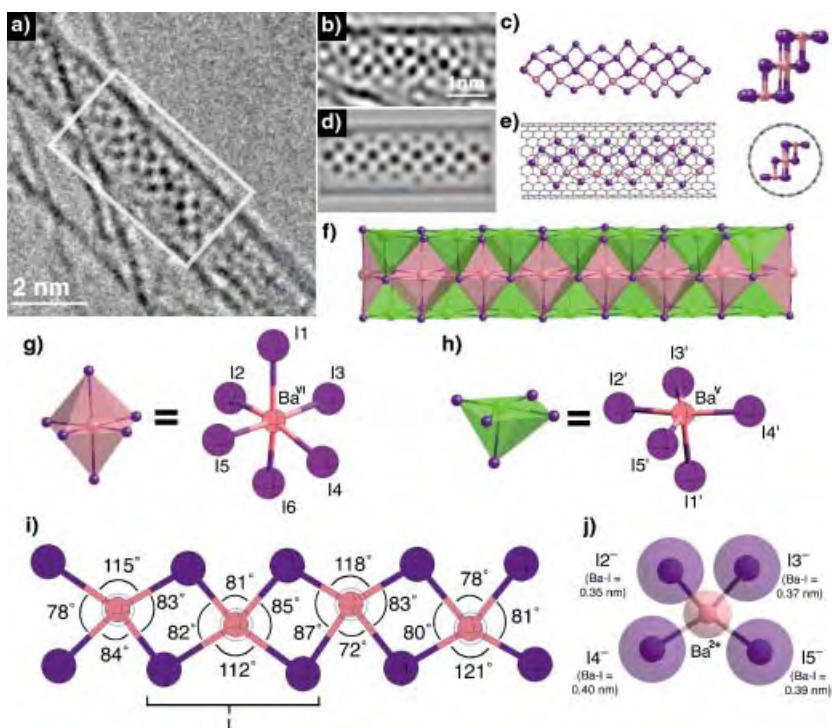


Figure 2. a) HRTEM image of BaI_2/SWNT composite. b) Detail from boxed region in (a), for which image noise was reduced with a deconvolution filter. c) Structure plot based on a 2D peak-mapping analysis of (b); end-on view on the right. d) Simulated HRTEM image. e) Complete structure model of BaI_2/SWNT composite. f) Coordination model of 1D BaI_2 chain. g) 5-coordinate, h) 6-coordinate BaI_6 polyhedra and ball-and-stick models derived from (c). i) and j) Models showing derived equatorial bond angles and distances for BaI_4 units along the center of the 1D BaI_2 chain (ionic radii in (j) indicated by diffuse spheres).

columns 1–3 atoms thick in projection, each of which may contain some combination of Ba and I. The columnar spacings in the fragment were typical of those observed in other BaI_2 -

filled SWNTs, and we believe that the crystal microstructure is therefore representative, although the microstructure of SWNT fillings is known to vary as a function of tube diameter.^[4, 5, 8]

To construct a model for the encapsulated crystal, a 2D peak-mapping program was used to determine the relative positions of the atomic columns in Figure 2b, and this produced the atom map shown in Figure 2c. To derive the complete crystal, the fragment was expanded vertically with respect to the plane of the page to give the end-on representation shown on the right of Figure 2c, in which the fragment can be visualized as being 1-2-3-2-1 atomic layers in thickness. Atomic positions were assigned on the basis of a coordination scheme for Ba and I which retains Ba in the +2 oxidation state. The vertical expansion was scaled to take into account the Ba–I bond length anticipated from the ionic radii of Ba^{VI2+} (0.136 nm)^[16] and I^{VI-} (0.22 nm),^[16] that is, 0.356 nm. A near-Scherzer focus simulated HRTEM image^[4] (Figure 2d), calculated from a composite crystal consisting of a 4 nm long section of a (12,12) SWNT^[17] and the derived crystal fragment (Figure 2e), provides good agreement with the experimental image. An end-on view of the composite is shown on the right of Figure 2e. A coordination polyhedra model derived from the 1D chain (Figure 2f) produces octahedral coordination for the Ba²⁺ ions along the center of the chain and pentagonal coordination for the Ba²⁺ ions on the edges of the chain (see also Figure 2g and h).

By combining information from the lattice image and the structural model, it is possible to derive information regarding I–Ba–I bond angles and distances within the 1D BaI₂ crystal. The equatorial I–Ba–I bond angles can be estimated from the spot dispositions in the lattice image (Figure 2b), as shown schematically for the representative fragment in Figure 2i. The apical Ba–I distances must be estimated from the ionic radii of Ba²⁺ and I⁻ (see above). The equatorial Ba–I distances can be estimated from the intercolumnar distances measured from the dark spots in the micrograph, and this gives values ranging from 0.35 to 0.40 nm (estimated error ± 0.02 nm), as shown for the representative polyhedra in Figure 2j. Any out-of-plane distortions will cause these distances to be longer, by inspection. Such expansions notwithstanding, the estimated Ba–I distances are either equal to or slightly longer than the apical Ba–I distance of 0.356 nm predicted from the ionic radii (see above). The close correspondence of these measured values with the predicted bond lengths is an important argument in favor of our model.

An exhaustive comparison of the experimental structure (shown in perspective view in Figure 1d) and all possible fragments derived from the structures in Figure 1a–c could only produce one approximate match with the experimental structure, shown in Figure 1e. Versions of this fragment can be derived from either the *Pnam* or *P6m* forms of BaI₂ (Figure 1a and b), although both have an excess of iodine due to lattice termination. It is therefore necessary to remove the atoms depicted in yellow in Figure 1e to restore the stoichiometry to BaI₂ (see Figure 1f). While this structure resembles that of the experimental fragment (Figure 1d), comparison of the end-on views of the two fragments reveals that the similarity is only superficial. The Ba²⁺ ions exist in a far more

compressed environment in the experimental fragment than in the derived fragment (cf. end-on views in Figure 1d and f). The extent of this difference is reflected in two key experimental observations: 1) the shortening of the Ba–Ba distance defined along diagonally related BaI_x polyhedra from 0.597 (*Pnam* form) or 0.588 (*P6m* form) to 0.49 nm; 2) the much more symmetrical coordination of iodine in the 1D chain. We conclude that the experimental 1D fragment has a crystal structure substantially different to any of the reported forms of BaI₂.

This work describes the structural characterization of a BaI₂ nanocrystal formed within a SWNT of 1.6 nm diameter by using a “bottom-up” approach. The obtained structure is found to have Ba in 5- and 6-coordination—both unknown in bulk BaI₂—in the form of a 1D chain consisting of edge-linked coordination polyhedra. This result represents a significant departure from those for previously described SWNT fillings,^[1–3] as it represents the first example for which all structural properties of an SWNT-encapsulated crystal are different from those of the bulk structure. It is anticipated that the physical properties of the derived 1D chain will be substantially modified as a result.

Experimental Section

A sample of as-prepared SWNTs, prepared according to a published catalytic arc-synthesis method,^[12] and a sample of highly pure anhydrous BaI₂ (Aldrich, 99.999%) were combined in 1:1 mass ratio. The mixture was ground using a pestle and mortar and then transferred to a silica quartz tube 6 mm in diameter. This procedure was performed under dry conditions in a glove box, due to the deliquescent nature of BaI₂. The quartz tube was then sealed under vacuum. The ampoule was heated at 1 K min⁻¹ to 40 K above the melting temperature of the salt (i.e., 740 °C) and held at this temperature for 5 h. The furnace was set to a slow cooling program (from 780 to 18 °C over 1 h) to allow for optimum growth of the salt crystals within the SWNTs.

The product was examined in a 300-kV JEOL JEM-3000F field emission gun HRTEM (point resolution 0.16 nm) equipped with a LINK “ISIS” X-ray microanalysis system. Images were acquired digitally on a Gatan model 794 (1 k × 1 k) CCD camera, the magnification of which was calibrated with Si[110] lattice spacings. Energy dispersive X-ray microanalysis (EDX) was performed with an electron probe 0.5 nm in diameter. Image simulations were performed by using a standard multislice algorithm incorporating representative parameters for our FEGTEM.

Received: November 15, 2001 [Z18221]

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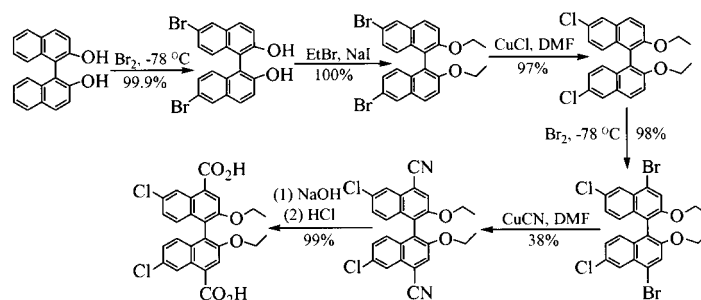
Rational Design of Homochiral Solids Based on Two-Dimensional Metal Carboxylates**

Yong Cui, Owen R. Evans, Helen L. Ngo, Peter S. White, and Wenbin Lin*

The design and construction of metal–organic coordination networks (MOCNs) have received significant attention in recent years, mostly motivated by the potential of generating tailor-made functional materials through molecular engineering of the constituent building blocks using the tools of modern synthetic chemistry.^[1] Indeed many MOCNs have been reported to exhibit interesting properties, which include functional-group or size-selective sorption,^[2] catalysis,^[3] gas storage,^[4] molecular recognition,^[5] and second harmonic generation.^[6] Among these, the synthesis of MOCNs with permanent porosity is by far the most fruitful, and many metal–carboxylate coordination networks with extremely large surface areas have been constructed, based on the secondary building unit (SBU) concept that has been extensively used in zeolite synthesis.^[7] Compared to zeolites and the recently developed MCM-type mesoporous materials,

MOCNs are built with weaker metal–ligand coordination bonds and are inherently less stable. It is thus imperative to incorporate functions that are not possible with inorganic oxide materials into MOCNs. Our recent success with crystal engineering of nonlinear-optical (NLO) materials based on MOCNs provides such an example.^[6] Another unique feature of MOCNs is the ability to design chiral pores and functionalities, which may be exploited in heterogeneous asymmetric catalysis and enantioselective separations.^[8] With a few exceptions,^[3b,c,9] the chiral MOCNs reported to date were synthesized from simple achiral components.^[10] The chirality of such MOCNs originates from the spatial disposition of their building blocks and is not amenable to fine tuning.^[1d] Moreover, the bulk materials of such MOCNs tend to be racemic and cannot be exploited for chirotechnology.^[11] A more straightforward approach to chiral solids relies on the use of metal ions or metal clusters as nodes, and chiral multifunctional ligands to link these nodes. Herein we report the rational synthesis of chiral two-dimensional (2D) networks, based on enantiopure dicarboxylate bridging ligands and metal–organic SBUs.

As illustrated in Scheme 1, enantiopure atropisomeric 6,6'-dichloro-2,2'-diethoxy-1,1'-binaphthylene-4,4'-dicarboxylic



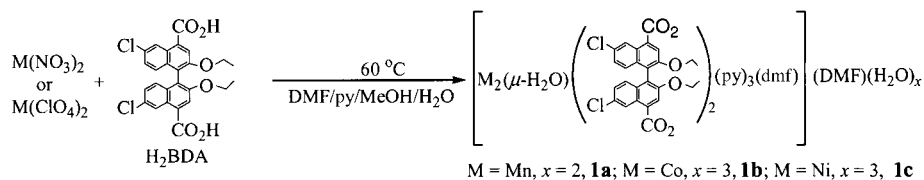
Scheme 1. Synthesis of 6,6'-dichloro-2,2'-diethoxy-1,1'-binaphthylene-4,4'-dicarboxylic acid (H₂BDA).

acid (H₂BDA), was prepared in six steps in good overall yield (35.7%), from the readily available chiral 1,1'-bi-2-naphthol (BINOL). Homochiral metal carboxylates with the general formula of [M₂(μ-H₂O)(bda)₂(py)₃(dmf)] · (DMF) · (H₂O)_x (M = Mn, x = 2, **1a**; M = Co, x = 3, **1b**; M = Ni, x = 3, **1c**) were obtained in moderate yields (31–42%), by treatment of metal nitrate or perchlorate salts with H₂BDA in a mixture of N,N'-dimethylformamide (DMF), MeOH, and pyridine (py) at 60 °C (Scheme 2). Compounds **1a–c** are stable in air, and insoluble in water and common organic solvents. The IR spectra of **1a–c** exhibited bands at 1660–1320 cm⁻¹ characteristic of carboxylate groups. Thermogravimetric analyses (TGA) show that **1a** loses 12.8% of its total weight on heating to 220 °C, which corresponds to the loss of three water molecules and two DMF molecules per formula unit (expected 12.7%). TGA indicate that **1b** and **1c** experience 13.7% and 13.3% weight losses by 220 °C, corresponding to the loss of four water molecules and two DMF molecules for both **1b** and **1c** (expected 13.9%). The formulations of **1a–c** are supported by microanalysis results.

[*] Prof. W. Lin, Dr. Y. Cui, O. R. Evans, H. L. Ngo, Dr. P. S. White
Department of Chemistry, CB#3290
University of North Carolina, Chapel Hill, NC 27599 (USA)
Fax: (+1) 919-962-2388
E-mail: wlin@unc.edu

[**] We acknowledge financial support from NSF (DMR-9875544). We thank Dr. Gary Enright for the X-ray powder diffraction patterns. W.L. is an Alfred P. Sloan Fellow, an Arnold and Mabel Beckman Young Investigator, a Cottrell Scholar of Research Corp, and a Camille Dreyfus Teacher-Scholar.

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



Scheme 2.

A single-crystal X-ray diffraction study^[12] performed on (*S*)-**1a** reveals an infinite 2D coordination network that crystallizes in the chiral space group $P2_12_12_1$. The asymmetric unit of **1a** consists of two Mn centers, two BDA groups, three pyridine molecules, two DMF molecules, and three water molecules. Each BDA ligand contains one bridging carboxylate group and one monodentate carboxylate group. The basic building unit for **1a** is a dimanganese carboxylate moiety (Figure 1), where the Mn1 and Mn2 centers are bridged by

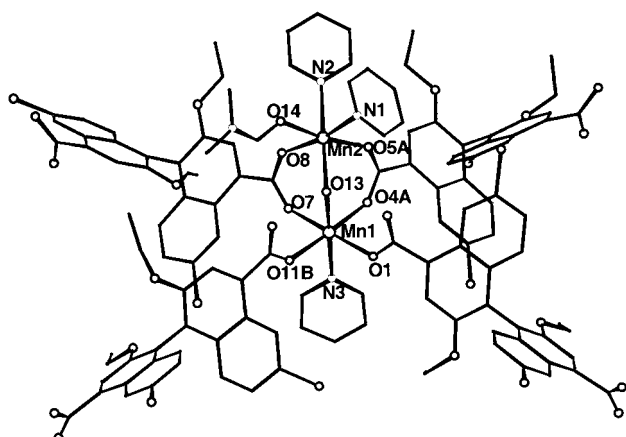


Figure 1. Coordination environment for the $[\text{Mn}_2(\mu\text{-H}_2\text{O})(\text{bda})_2(\text{py})_3\text{-(dmf)}]$ building block in **1a**. Only one part of the disordered ethyl group of the BDA anion is shown, and the DMF and water guest molecules are omitted.

two carboxylate groups of two different BDA ligands and one water molecule, with a $\text{Mn1} \cdots \text{Mn2}$ distance of 3.710(1) Å. The water molecule bridges the Mn centers in a slightly unsymmetrical fashion with the $\text{Mn1}-\text{O13}$ distance of 2.334(3) Å and the $\text{Mn2}-\text{O13}$ distance of 2.230(3) Å. There are two monodentate carboxylate groups of two other BDA ligands around the dimeric core (Figure 1). The remainder of the coordination environments of the Mn1 and Mn2 centers is completed by three pyridine molecules and one DMF molecule. Both Mn1 and Mn2 adopt a slightly distorted octahedral coordination geometry; the Mn1 center coordinates to two bridging carboxylate O atoms and two monodentate carboxylate O atoms of four BDA groups, one bridging water molecule, and one pyridine molecule, while the Mn2 center coordinates to two bridging carboxylate O atoms of two BDA groups, one bridging water molecule, one DMF molecule, and two pyridine molecules. The *cis*-bond angles around the Mn1 center range from 85.9(2) to 96.3(2)°, while the *cis*-bond angles around the Mn2 center range from 82.0(2) to 101.6(2)°. The dihedral angles between the two binaphthyl subunits of the DBA ligands are 93.9 and 94.2°.

The dimanganese cores are linked by four *exo*-tridentate BDA ligands to four adjacent dimanganese cores to result in a 2D neutral rhombohedral grid in the *bc* plane with a (4,4) topology (Figure 2a). The short and long diagonals of the rhombohedral grid run along the *b* and *c* axis,

respectively. The carboxylate groups on the 4,4'-positions of BDA ligands behave as rigid linear linkers, and allow the formation of 2D rhombohedral grids. A space-filling representation of **1a** (Figure 2b) clearly demonstrates the formation of chiral cavities. Interestingly, the ethoxy-protected

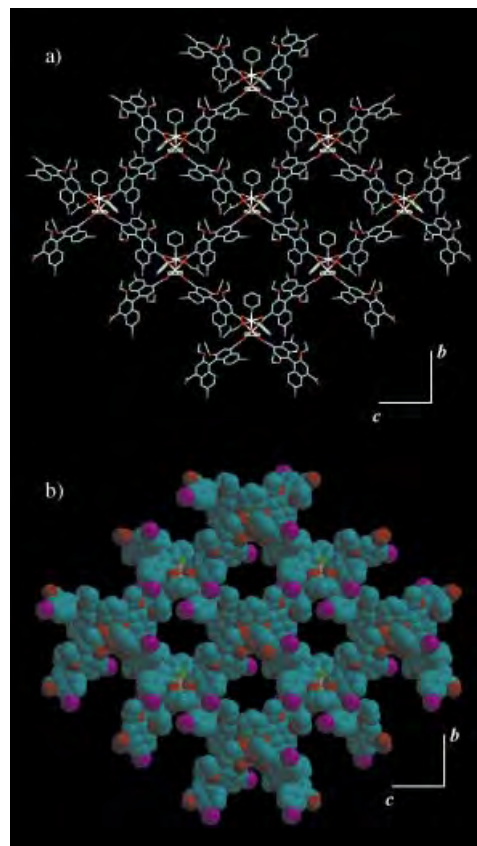


Figure 2. a) A view of 2D rhombohedral grid of **1a** down the *a* axis; b) A space-filling model of **1a**, viewed down the *a* axis. The DMF and water guest molecules are omitted for clarity.

BINOL functionalities point towards the open cavities. It is important to note that BINOL is well established in the organic community as a beneficial chiral auxiliary for a variety of highly enantioselective homogeneous asymmetric catalyses.^[13] The ability to place such a useful chiral auxiliary inside an open channel of well-characterized, crystalline, porous MOCN represents a major step towards the rational synthesis of crystalline chiral porous materials. Unfortunately, a careful examination of the structure of **1** shows that the 2D grids stack on top of each other in a staggered arrangement along the *a* axis (Figure 3). The adjacent layers are shifted by $\frac{1}{2}b$ and $\frac{1}{2}c$ along the *b* and *c* axes, respectively, and have a layer-to-layer separation of 7.45 Å ($\frac{1}{2}a$). Such a staggered arrange-

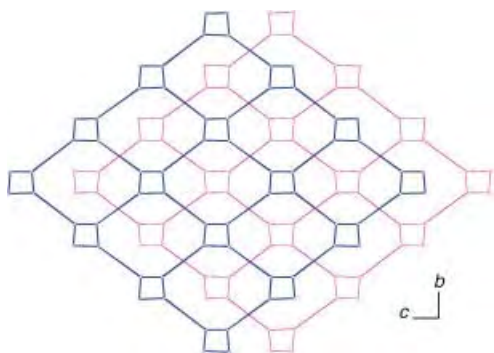


Figure 3. A schematic showing the staggered arrangement of adjacent 2D rhombohedral grids of **1a**. The dimanganese cores are represented by smaller quadrangles (comprised of the four carbon atoms of the four coordinating carboxylate groups), while the BDA linkers are represented by the longer lines.

ment positions the dimanganese core from an adjacent layer in the open cavity of the 2D rhombohedral grid. Consequently, compound **1** has a minimal void space, which is occupied by one DMF and two water guest molecules. Finally, the bridging water molecule forms strong intramolecular hydrogen bonds with the uncoordinated oxygen atoms of two monodentate carboxylate groups of the BDA ligands, as indicated by O...O distances of 2.613(1) and 2.647(1) Å.

A single-crystal X-ray structure determination reveals that (*S*)-**1b** is isostructural to (*S*)-**1a**,^[12] while cell parameter determinations and powder X-ray diffraction studies establish that (*S*)-**1c** is also isostructural to (*S*)-**1a**.^[14] The phase purity for the bulk samples of **1a–c** has been established by comparison of their observed and simulated X-ray powder diffraction patterns. We have also prepared Co compound **1b** using the (*R*)-enantiomer of 6,6'-dichloro-2,2'-diethoxy-1,1'-binaphthyl-4,4'-dicarboxylic acid. Solid-state (circular dichroism) CD spectra of compound **1b** made from (*R*)- and (*S*)-H₂DBA are exact mirror images of each other, and demonstrate that when compound **1b** is made from either (*R*)- or (*S*)-H₂BDA, supramolecular enantiomers result. Solid-state CD spectra of compound (*S*)-**1a** and (*S*)-**1c** are similar to that of (*S*)-**1b**.

In conclusion, we have developed a rational synthetic approach toward homochiral solids, based on 2D coordination networks and using enantiopure dicarboxylate ligands and dimetal SBUs as the building blocks.

Experimental Section

Full experimental details are given in the Supporting Information. Synthesis of **1a–c**: A mixture of Co(ClO₄)₂·6H₂O, Mn(NO₃)₂·6H₂O, or Ni(NO₃)₂·6H₂O (0.005 mmol) and H₂BDA (0.005 mmol) was placed in a small vial containing DMF (2.5 mL), H₂O (0.5 mL), MeOH (0.5 mL), and pyridine (0.5 mL). The vial was sealed, heated at 60 °C for 16 h, and allowed to cool to room temperature. The crystals which were suitable for X-ray diffraction were collected by filtration, washed with diethyl ether, and dried in air. Yield: **1a**, 0.058 g, 42%; **1b**, 0.050 g, 37%; **1c**, 0.035 g, 31%. IR and analytical data: **1a**: elemental analysis (%) calcd for C₇₃H₇₁Mn₂N₅O₁₇: C 56.86, H 4.64, N 4.54; found: C 56.09, H 4.17, N 3.90; IR: $\tilde{\nu}$ = 3442 (m), 2978 (w), 2926 (w), 1653 (s), 1642 (m), 1624 (s), 1578 (s), 1492 (m), 1445 (ms), 1401 (s), 1323 (s), 1222 (ms), 1117 (m), 1091 (ms), 1060 (m), 1045 (m), 906 (w), 868 (w), 822 (w), 800 (m), 744 (ms), 698 (m), 678 (w), 625 (w) cm⁻¹. **1b**: elemental analysis (%) calcd for C₇₃H₇₃Co₂N₅O₁₈: C 55.91, H 4.69, N 4.47; found: C 55.52, H 4.14, N 3.88; IR: $\tilde{\nu}$ = 3433 (m), 2978 (w), 2927 (w), 1657

(ms), 1641 (m), 1627 (s), 1580 (s), 1492 (m), 1445 (ms), 1402 (s), 1322 (s), 1222 (ms), 1117 (m), 1091 (ms), 1060 (m), 1042 (m), 907 (w), 868 (w), 822 (w), 799 (m), 740 (ms), 700 (m), 630 (w) cm⁻¹. **1c**: elemental analysis (%) calcd for C₇₃H₇₃Ni₂N₅O₁₈: C 55.93, H 4.69, N 4.47; found: C 54.15, H 4.31, N 3.90; IR: $\tilde{\nu}$ = 3447 (m), 2980 (w), 2928 (w), 1655 (ms), 1642 (m), 1628 (s), 1579 (s), 1491 (m), 1445 (ms), 1402 (s), 1322 (s), 1222 (ms), 1118 (m), 1091 (ms), 1060 (m), 1042 (m), 907 (w), 868 (w), 822 (w), 799 (m), 750 (ms), 699 (m), 631 (w) cm⁻¹.

Received: October 15, 2001 [Z18062]

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- X-ray single-crystal diffraction data for both **1a** and **1b** were collected on a Siemens SMART CCD diffractometer. Crystal data for **1a**: orthorhombic, space group *P*₂₁₂₁₂, *a* = 14.891(1), *b* = 19.906(1), *c* = 24.500(1) Å, *V* = 7262.3(4) Å³, *Z* = 4, ρ_{calcd} = 1.41 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 0.567 mm⁻¹. Least-squares refinement based on 17348 reflections with *I* > 2σ(*I*) and 851 parameters led to convergence, with a final *R*1 = 0.072, *wR*2 = 0.193, and *GOF* = 1.09. Flack parameter = 0.04(2). Crystal data for **1b**: orthorhombic, space group *P*₂₁₂₁₂, *a* = 14.710(5), *b* = 18.992(1), *c* = 24.783(1) Å, *V* = 7286.6(3) Å³, *Z* = 4, ρ_{calcd} = 1.42 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 0.687 mm⁻¹. Least-squares refinement based on 15985 reflections with *I* > 2σ(*I*) and 855 parameters led to convergence, with a final *R*1 = 0.104, *wR*2 = 0.233, and *GOF* = 1.14. CCDC-177733 (**1a**) and CCDC-177734 (**1b**) contains the supplement-

tary crystallographic data for this paper. These data can be obtained free of charge via 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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 [14] Unit cell parameters for **1c**: orthorhombic, $a = 14.29(2)$, $b = 19.97(4)$, $c = 23.96(4)$ Å, $V = 6834(16)$ Å³.

Inorganic Chemistry Goes Protein Size: A Mo₃₆₈ Nano-Hedgehog Initiating Nanochemistry by Symmetry Breaking**

Achim Müller,* Eike Beckmann, Hartmut Bögge,
Marc Schmidtman, and Andreas Dress

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

Nature's evolution from the primordial Earth through to the present overwhelming variety of macroscopic forms and functionalities, the formation of which is directed by their molecular "counterparts", that is, by nanosized biomolecules, should stimulate thoughts about the potential of material systems in general as well as related basic first principles or natural laws.^[1] We refer to processes based on reservoir systems containing appropriate building blocks, the linking of which can lead to an overwhelming or even infinite variety of molecular forms including those showing symmetry breaking. This process is particularly valid on entering the nanocosmos size category.^[2] The nanocosmos as such, does not show the variety-limiting translational symmetry restriction of macroscopic crystalline materials but offers—in contrast to the microcosmos with its small molecules—the possibility that (several) larger arrays with local symmetries are not in agreement with the overall symmetry—a situation well known for spherical viruses (see Figure 1 and ref. [3])—can occur. This increases the options for the generation of an extreme structural versatility. Thus, the appropriate building units must display a certain type of flexibility as prerequisite for linking versatility (of course not coming close to that of amino



Figure 1. A drawing of a $T=3$ icosadeltahedron—as model for the topologically identical coat protein subunits of the Tomato Bushy Stunt Virus (TBSV)—showing its arrangement of three quasi-equivalent sets of 60 icosahedrally related subunits (lobes/proteins). The orange lobes pack about the icosadeltahedron's exact fivefold axes, whereas the blue and green lobes alternate about its local sixfold axes (reproduced with permission from ref. [3]).

acids), a condition well fulfilled by molybdenum oxide based fragments/aggregates. These special entities, abundant as (virtual) building units in a potential "dynamic library",^[4,5] can, by a type of "split-and-link process", adapt their size and shape depending upon slight alterations of the relevant boundary conditions;^[6-8] evident reasons for this "molybdate" specific quality are listed in footnote ref. [9]. This versatility could lead us, to use a term from J.-M. Lehn lectures, to the category "Multiple Expression of Molecular Information", a statement also supported by the variety of giant clusters obtained from relevant "libraries".^[6-8] Here we report the formation of a rather unusual giant molybdenum oxide based nanocluster, the size of hemoglobin (diameter approximately 6 nm), and containing 368 metal (1880 non-hydrogen) atoms formed by the linking of 64 {Mo₁}-, 32 {Mo₂}-, and 40 {Mo-(Mo₃)}-type units by a remarkable symmetry-breaking process which is nicely recognizable at the cluster surface. The understanding of the present process will be the starting point for the synthesis of quite a number of other "size comparable" clusters and reactions of these. Here we refer to a far-reaching step into the nanocosmos with perspectives for nanochemistry through symmetry breaking, molecular topology, and surface sciences with catalytical and topological relevance. Symmetry breaking will be referred to in relation to transitions from positive to negative surface areas which can be considered as model for nature's patternings or breaking monotony.

By reducing a molybdate solution which is acidified with sulfuric acid, the deep-blue compound **1** containing the giant mixed-valence cluster anion **1a** (Figure 2) is obtained which was characterized by elemental analysis (including redox titrations to determine the (formal) number of Mo^V centers), thermogravimetry (to determine the actual crystal-water content which is important for the analyses), bond valence

[*] Prof. Dr. A. Müller, Dipl.-Chem. E. Beckmann, Dr. H. Bögge, M. Schmidtman
 Lehrstuhl für Anorganische Chemie I
 Fakultät für Chemie der Universität
 Postfach 100131, 33501 Bielefeld (Germany)
 Fax: (+49)521-106-6003
 E-mail: a.mueller@uni-bielefeld.de
 Prof. Dr. A. Müller, Prof. Dr. A. Dress
 Fakultät für Mathematik und Graduiertenkolleg (GK) "Strukturbildungsprozesse", Universität Bielefeld
 [**] Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the European Union (HPRN-CT 1999-00012) and the GK is gratefully acknowledged.

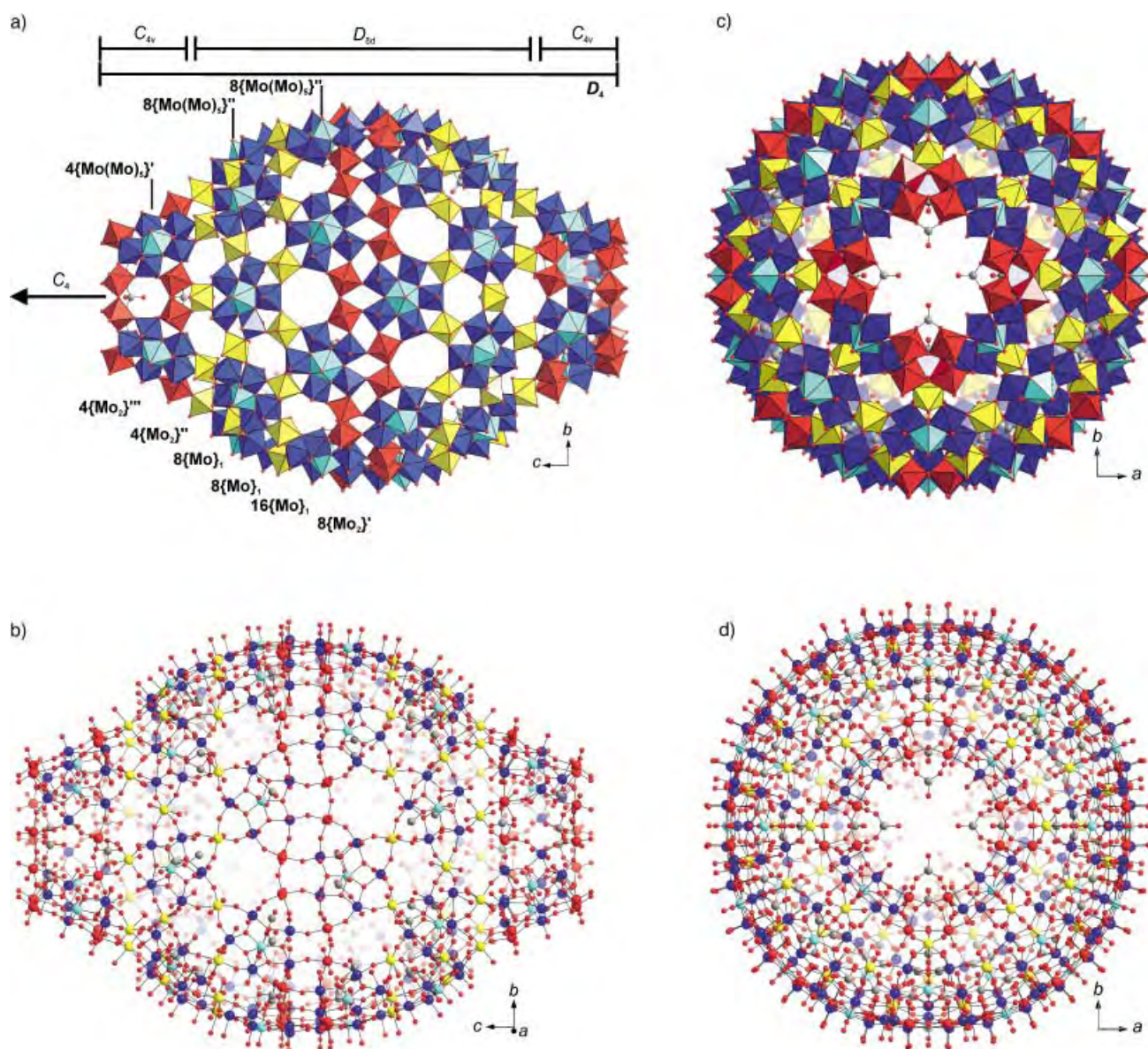
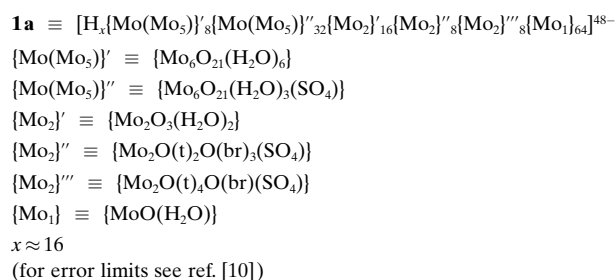
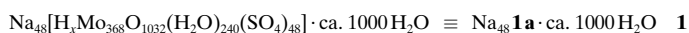


Figure 2. Structure of **1a** in crystals of **1** in polyhedral (a) and ball and stick (b) representation perpendicular to the C_4 axis and along the C_4 axis ((c) and (d); building units $\{Mo_1\}$ yellow, $\{Mo_2\}$ red, $\{Mo(Mo_5)\}$ blue with blue-turquoise pentagonal bipyramids; O atoms small red spheres, S atoms gray spheres). Note that one capping part is turned against the other by $360/16^\circ$. The different building blocks and the arrays of different local symmetry are assigned.

sum (BVS) calculations, spectroscopic methods (IR, resonance Raman, Vis/nIR) as well as single-crystal X-ray structure analysis.^[10]



Compound **1** crystallizes in the space group $I4mm$ and in the unit cell contains two giant hedgehog-like cluster anions

1a which have approximate D_4 symmetry with a central ball-shaped fragment $\{Mo_{288}O_{784}(H_2O)_{192}(SO_4)_{32}\}$ (B) and two capping units $\{Mo_{40}O_{124}(H_2O)_{24}(SO_4)_8\}$ (C). Remarkably, there are three rather large areas, that is, two C and one B, with different local symmetries (see Figure 2 and Addendum after Experimental Section).^[11, 12] More precisely, **1a** is built up by the six above mentioned well-defined building units (see also Figure 1), while a giant molecular container with a huge cavity (diameter $\approx 2.5 \times 4.0$ nm at its most extended points) is formed offering space, for the tremendously large number of about 400 H_2O molecules. (The number of water molecules in the crystal given above (1000) includes the 400 molecules encapsulated.) The presence of the bidentate SO_4^{2-} ligands (see formulas) can also be shown by

the typical splitting of the $\nu_3(\text{F}_2)$ -type vibrational bands (1191, 1122, 1060 cm^{-1}), and the abundance of Mo^{V} as well as Mo^{VI} centers by the IVCT (intervalence charge transfer) band at ~ 740 nm. The comparably large number of different building units of **1a** can be identified from Figure 2 together with the above given formulas. The two types of $\{\text{Mo}(\text{Mo}_5)\}$ units differ in the number and coordination type of the SO_4^{2-} ligands: 40 with SO_4^{2-} ligands and eight without located in the C_{4v} areas. The dinuclear units $\{\text{Mo}_2\}$ not only differ with respect to the number of bidentate SO_4^{2-} ligands (see formulas) but also, for those at the ends of both C caps, that is, the borderlines, both Mo centers have two terminal O atoms, a situation characteristic for stopping growth. The $\{\text{Mo}_1\}$ units are of the classical type $\{\text{OMo}^{\text{V}}(\text{H}_2\text{O})\}^{3+}$ and contribute correspondingly to the highly reduced state of **1a**. The other formal “ Mo^{V} -type centers” are distributed over several parts of the cluster areas, which causes a widespread delocalization of the Mo 4d electrons.

The structure of **1a** can be considered as a hybrid between the giant wheel ($\{\text{Mo}_{176}\}$ -type) and ball ($\{\text{Mo}_{102}\}$ -type) clusters.^[7b, 8, 13] We find in **1a** the $\{\text{Mo}(\text{Mo}_5)\}$ and $\{\text{Mo}_1\}$ units of the $\{\text{Mo}_{102}\}$ ball-type cluster as well as $\{\text{Mo}(\text{Mo}_5)\}$ and $\{\text{Mo}_2\}$ units of the wheel-type species. The hybrid character is—referring to the terminology of ref. [13]—also manifest by the occurrence of 24 C_5 -type $\{\text{Mo}_{11}\}$ groups of the ball-type clusters^[13] together with the related wheel (same type) 16 C_5 -type $\{\text{Mo}_{10}\}$ groups with only one MoO_6 octahedron less. Note that the two groups have 56 MoO_6 octahedra in common (Figure 3). Whereas the C_5 - $\{\text{Mo}_{11}\}$ groups are identical to those of the spherical ball-type clusters,^[13] the structure of the $\{\text{Mo}_{10}\}$ units of **1a** is identical to that of the $\{\text{Mo}_{10}\}$ fragment of the wheel-type cluster C_5 - $\{\text{Mo}_{11}\}$ unit, which, when compared to the symmetrical ball situation, has only the 11th octahedron displaced.^[14]

The high reduction state (ca. 112 Mo^{V} , 256 Mo^{VI}), which is much higher than that in the wheel systems (e.g., 28 Mo^{V} , 126 Mo^{VI}), reflects that reducing conditions favor cluster growth. (The largest cluster in acidified molybdate solution is, in absence of a reducing agent, the “rather small” $\{\text{Mo}_{36}\}$ anion^[15, 16] which “starts growing” upon reduction.^[8]) A negative charge or an increase in negative charge does not only prevents uncontrolled linking, but initiates further protonation as a prerequisite for further linking. The negative charge in the present case is supported by the abundance of SO_4^{2-} ligands coordinated to the intermediates and the final cluster species. This situation does not occur in presence of much weaker coordinating ligands, such as Cl^- or ClO_4^- ions: in cases where HClO_4 or HCl are used as acidification agents instead of H_2SO_4 not **1a**, but pure molybdenum oxide based wheel-type species are formed.^[8] For the present results it is important that the coordination ability of the SO_4^{2-} is not too strong (e.g., as it would be in the case of PO_4^{3-}) thus allowing a flexibility of coordination with the consequence that a variety of different appropriate building blocks can be generated. The average reduction state of the two Mo_{40} -type caps C of **1a** is lower than that of the D_{8d} part B. This observation agrees with our hypothesis that growing processes in POM-type systems are mostly based on nucleophiles which start “growing” by directing the formation of electrophiles (in a relative consid-

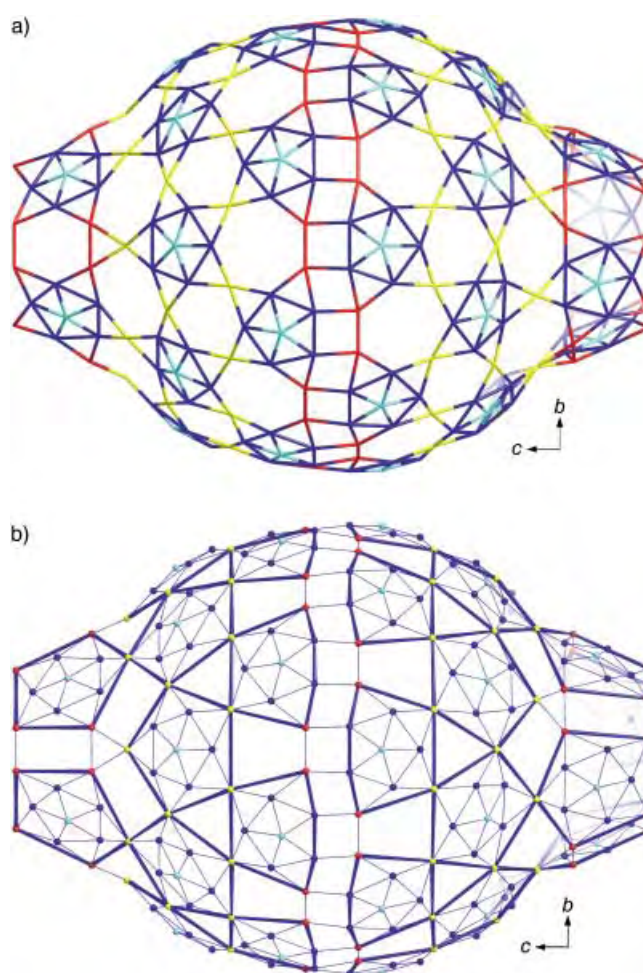


Figure 3. $\{\text{Mo}_{368}\}$ metal atom framework of **1a** in wire-frame (a) and in ball and stick representation with $\{\text{Mo}_{11}\}$ and $\{\text{Mo}_{10}\}$ building blocks emphasized through thick lines (b; color code as in Figure 2).

eration!) with which they get capped.^[17] In the present case, the central B part probably directs the formation of the C type units (see also ref. [18]).

Our prediction is that the knowledge of structural details of cluster **1a** will be the starting point for the synthesis of many others of comparable size as well as for a new type of nanochemistry which will allow *well defined* reactions to be performed at *well defined* sites of *well defined* nanoobjects, and includes their handling as intact units, for instance for cross-linking or preparation of composites, for example, with silica or surfactants, which is possible with these types of clusters as shown in case of the giant ball- and wheel-type species with the generation of micelles, films, and even liquid crystals.^[20] The present results are relevant for catalysis as it is still a challenge to understand details of the interaction mechanisms of substrates with the surfaces of heterogeneous catalysts.^[21, 22] In the case of transition metal oxides, such as MoO_3 , which play an important role in selective oxidation processes,^[22] it would be a tremendous step to consider the surfaces of discrete and well defined giant molybdenum oxide based clusters for model reactions relevant for related catalytically active bulk materials, the surface of which is difficult to investigate^[23, 24] (note that the large surface of **1a**

contains only Mo=O and Mo(H₂O) groups). Another interesting aspect is the possibility to perform supramolecular chemistry inside the cavity of the giant molecular container **1a**—the largest structurally well defined one known—as was possible with the smaller ball-type clusters.^[7c] Remarkably, this type of nanochemistry/nanotechnology and supramolecular engineering is based on structurally well-defined objects obtained by the “bottom-up” method.^[25, 26] Last but not least, the symmetry breaking^[11]—“visible” at the surface of **1a** because of the abundance of different large local symmetry areas or negative curvature in between positive curvatures at a giant cluster’s surface as in case of Fowler’s Phantasmagorical Fullerooids (see Addendum)—has model character for nature’s patterning processes in general and, in particular, those occurring within nucleation processes. Symmetry breaking is of fundamental importance for the understanding of patternings in the macroworld (in this respect the antagonistic effect actions are important) which was described by D’Arcy Thompson in his book “*On Growth and Form*”^[27c] (for general references see Ref. [11, 27, 28]). In this respect it would be a breakthrough if rather large nanoareas such as B and C with different symmetry could be extended further. In particular, this should be possible under dissipative conditions.

In any case, the formation of **1a** under conservative conditions shows a type of patterning, emergence, and complexity on the nanolevel, though not on the macrolevel, as for instance in case of the dissipative self-organizing model processes leading to Bénard-convection cells and Belousov-Zhabotinsky-type patternings (see ref. [27]). The novelty of the formation of the present nanoobject is that, in spite of its enormous size, a breaking of monotony during growth is observed. This breaking is caused by different distributions of a rather large number of different “negative and positive” vertices with polygons ranging from triangles to heptagons (see Addendum and Figure 4). The complexity here is nicely recognized by comparison with the Archimedean solids having only one type of vertex.

Experimental Section

Na₂S₂O₄ (0.15 g, 0.86 mmol) as reducing agent was added to a stirred solution of Na₂MoO₄ · 2H₂O (3 g, 12.4 mmol) in water (10 mL) which was acidified with 0.5 M H₂SO₄ (35 mL; immediate color change to blue). The solution was stored in a closed flask and after 2 weeks the precipitated deep-blue crystals of **1** were collected by filtration, yield: 80 mg (two crystal types: major part showing from top view a characteristic form like an elongated benzene molecule, while a much smaller fraction of the crystals is grown together). Characteristic IR bands (KBr pellet): $\tilde{\nu}$ = 1616 (m, δ (H₂O)), 1191 (w), 1122 (w), 1060 (all ν_{as} (SO₄)), 975/954 (s) (ν (Mo=O)), 761 (s), $\approx$ 700 (sh), 627 (w), 555 (m), 464 (w) cm⁻¹; approximate wavenumbers of the very broad Raman bands (KBr dilution; λ_e = 1064 nm): $\tilde{\nu} \approx$ 810 (m), 680 (w), 460 (m) cm⁻¹; Vis (in H₂O): $\lambda \approx$ 740 (very broad) nm.

Addendum

Combinatorial topology of the nanoclusters polyhedral structure relevant for the present surface and symmetry breaking complexity problem: The following section explains first of all the topological nature of the surface of **1a** but could also be of help for the chemist in constructing rather large patterns showing positive and negative curvatures. A combinatorial analysis of the four-regular polyhedral net defined by the Mo atoms of

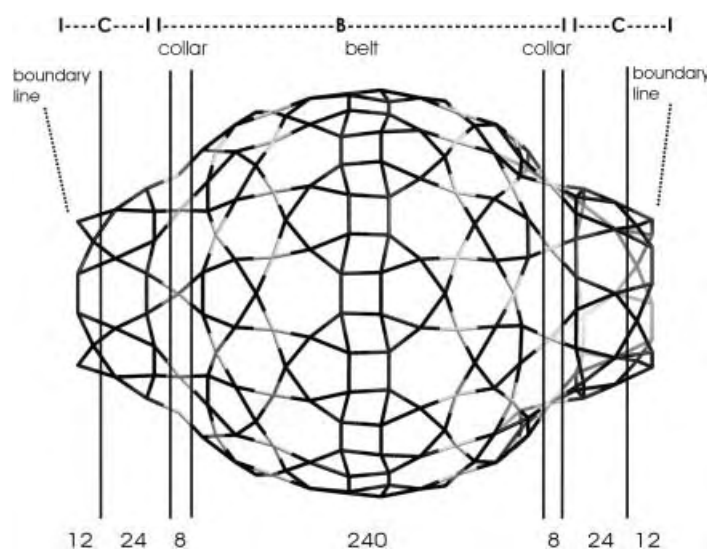


Figure 4. The four-regular polyhedron depicting the surface of **1a**, consisting of 328 = 368 – 40 Mo atoms (i.e. without the Mo atoms of the pentagonal bipyramids); it exhibits 64 vertices in the belt region, 32 with vertex configuration [3,4,4,5], and 32 of type [3,4,4,7], 16 + 8 of type [3,5,3,7], 8 of type [3,5,3,6], and 16 of type [3,6,3,7] in each of the two B regions next to the belt and another two times 16, 8, and 16 of type [3,5,3,6], [3,6,3,7], [3,5,3,7], respectively, next to the two collars, altogether 16 of type [3,7,3,7] along the two collars, and 8 of type [3,6,3,7], [3,5,3,7], and [3,5,3,6] each in the interior of the two capping regions, and 4 of type [3,5,3] and 8 of type [3,6] along each of the two boundary lines.

1a, as shown in Figure 4 (suppressing however, for simplicity, the Mo atoms within the interior of the pentagonal bipyramids) reveals a clear correspondence between the overall distribution of positively and negatively curved surface segments and the distribution of vertices with positive and negative combinatorial curvature. This observation is in agreement with Euler’s celebrated theorem^[31] interpreted as a discrete version of the equally celebrated Gauss – Bonnet theorem^[32] (see Figure 5 and 6 as illustrative examples of positively and negatively curved surfaces).

Indeed, the interior of region B with D_{8d} and of the two capping regions C with C_{4v} symmetry are positively curved; however, these are connected by the two narrow collars exhibiting a strong indentation, thus creating two ring-shaped surface components of large negative curvature of relevance for the symmetry breaking. Additional negative curvature is “hidden” in the jaggedness of the two circular boundary lines (indeed, straightening them out into perfect circles would create shapes that would each mimic the shape of a neck, that is, one half of the negatively curved inner part of a torus, see Figure 5). Correspondingly, the average combinatorial curvature (definition in ref. [33]) of the 240 Mo atoms in the interior of B is +4/315 while the same holds for the 48 (24 + 24) Mo atoms in the interior of the two capping regions; in contrast, it is –30/315 for each of the 16 (8 + 8) Mo atoms in the two collars and –28/315 for each of the 24 (12 + 12) Mo atoms in the two jagged circular boundary lines.^[34] Clearly, this is in perfect agreement with the positive curvature observed in the major parts of B and

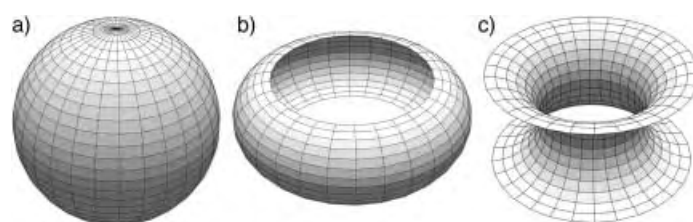


Figure 5. Shapes of positively (a) and (b) and negatively (c) curved surfaces. The sphere and the outer part of a torus are paradigms of surfaces exhibiting positive curvature (a) and (b), the saddle and the inner part of a torus are paradigms of surfaces exhibiting negative curvature (c).

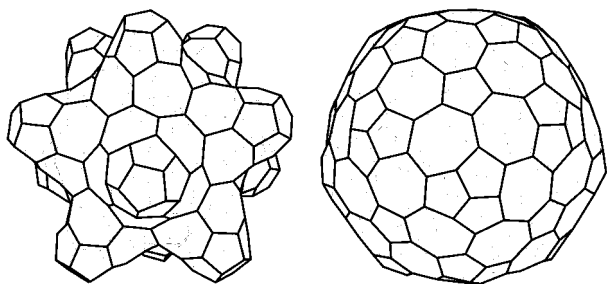


Figure 6. The shown Fowler's Phantasmagorical Fulleroids are text book examples illustrating how areas exhibiting strongly positive curvature can be intertwined with areas exhibiting negative curvature to produce a surface of only moderately positive curvature. Any fulleroid with icosahedral symmetry consisting of only pentagons and heptagons contains exactly $12 + 60N$ pentagons and $60N$ heptagons, for some positive integer N . There are two such fulleroids with $N=1$: a) where the 72 pentagons come in 12 clusters of 6 pentagons each generating *outcrops* of high positive curvature counterbalanced by a network of negatively curved *channels* built from its 60 heptagons, which results in a net positive curvature of four as required, b) consisting of 12 single pentagons and 20 clusters of three pentagons each, also connected by a network of negatively curved channels built from the heptagons exhibiting, however, a much smoother geometry because of the much better local balance of positive and negative curvature.

C, being counterbalanced by the considerably stronger negatively curved collars of B and boundary lines of C. Our analysis implies also that, for purely geometric reasons, the nanocluster's shape could not have been built up without the use of, at least, some heptagons counterbalancing the positive curvature implied by the pentagonal building blocks, at least as long as two triangles (or just one triangle and two quadrangles) occur at each interior vertex among the four polygons incident with that vertex (see also Figure 6a). Remarkably, the negative curvature at the two jagged boundary lines of C stops the growth process.

Received: November 15, 2001 [Z18228]

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- [5] Important in this context is that virtual building blocks, e.g. those abundant as fragments of larger units, become available for linking under special boundary conditions. The relevant process is of the category "split and link". An interesting example refers to the important pentagonal unit of the type $\{\text{Mo}(\text{Mo}_5)\}$ also occurring in **1a**. Its existence within larger fragments was known from many compounds, for instance in those of the $[\text{Mo}_{36}]$ and $[\text{Mo}_{57}]$ type^[6] and even in extended solid-state structures (N. N. Greenwood, *Ionic Crystals, Lattice Defects and Non Stoichiometry*, Butterworth, London, **1968**). Therefore, the pentagonal unit should also exist as a transferable unit especially because of its high symmetry and because its atoms are

densely packed (all polyhedra linked by edges). This finally led to the discovery of the spherical ball system with 12 of these units spanning an icosahedron.^[7a] Furthermore, this unit is important for the generation of a large number of nanoclusters with curvatures like the present one (see Addendum).

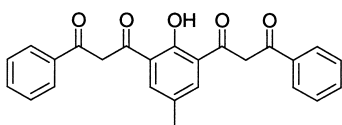
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- [9] Important factors are, the easy change of coordination numbers as well as the easy exchange of H_2O ligands at Mo-sites—not too strong and not too weak Mo–O–Mo-type bonds allowing the "split-and-link" process (these are even "tunable" by alterable boundary conditions, i.e. the reducing conditions)—easy change of electron densities not only within the Mo–O bonds but also at the O sites (important for protonation) depending on the redox conditions which increases the linking versatility of specific groups—no strong tendency to form metal–metal bonds, which limits the structural versatility, as is the case of tungsten—and last but not least, the presence of terminal Mo=O groups protecting unlimited growth to extended structures. Important: we refer here in this context to mixed valence compounds of type III (complete electron delocalization) in the of Robin and Day classification. (The fundamental compound types are discussed e.g. in: "Mixed Valency Systems: Applications in Chemistry, Physics and Biology" (Ed.: K. Prassides), Kluwer, Dordrecht, **1991**).
- [10] Crystal data for **1** $\text{H}_{2496}\text{Mo}_{368}\text{Na}_{48}\text{O}_{2464}\text{S}_{48}$, $M = 79888.16 \text{ g mol}^{-1}$, tetragonal, space group $I4mm$, $a = 43.4648(13)$, $c = 69.393(3) \text{ Å}$, $V = 131097(8) \text{ Å}^3$, $Z = 2$, $\rho = 2.023 \text{ g cm}^{-3}$, $\mu = 1.856 \text{ mm}^{-1}$, $F(000) = 77920$, crystal size $= 0.20 \times 0.15 \times 0.10 \text{ mm}^3$. Crystals of **1** were removed from the mother liquor and immediately cooled to 163(2) K on a Bruker AXS SMART diffractometer (three circle goniometer with 1 K CCD detector, MoK_α radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width in three runs with 606, 435, and 230 frames ($\phi = 0, 88$ and 180°) at a detector distance of 5 cm). A total of 211056 reflections ($0.66 < \theta < 20.03^\circ$) were collected of which 32441 reflections were unique ($R(\text{int}) = 0.1326$). An empirical absorption correction using equivalent reflections was performed with the program SADABS. The structure was solved with the program SHELXS-97 and refined using SHELXL-93 to $R = 0.0768$ for 23699 reflections with $I > 2\sigma(I)$, $R = 0.1233$ for all reflections; max./min. residual electron density 1.837 and -1.490 e Å^{-3} . (SHELXS/L, SADABS from G. M. Sheldrick, University of Göttingen **1997/93**; structure graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, **2001**.) 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-412283. The number of "crystal" H_2O molecules of the formula corresponds to the unit cell volume and is the maximum possible number regarding the space left. (This corresponds to our usual procedure as these types of compounds continuously release crystal water as a result of weathering.) The given number of protonations in the formula correlates with the analytically determined values of the (formal) number of Mo^V centers (112), and the found Na value. Whereas these values have a small error limit, the number of SO_4^{2-} ligands could—though they are disordered—be accurately determined according to the excellent agreement between results from elemental analysis and the single-crystal X-ray structure data. The H atoms disordered at (many) sulfate sites cannot be located.
- [11] See H. Genz, *Symmetrie und Symmetriebrechung in der Physik*, Vieweg, Braunschweig, **1991**; H. Haken, *Synergetics*, 3rd ed. Springer, Berlin, **1983**; K. Mainzer, *Thinking in Complexity*, 3rd ed., Springer, Berlin, **1997**.
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- [17] Examples are the transitions from the hypothetical highly negatively charged V^{IV} based Keggin unit to an extended stable one by its capping with six VO^{2+} additional groups,^[6,7b] (see also A. Müller et al., *Inorg. Chem.* **1997**, *36*, 5239–5250) from a $\{Mo_{37}\}$ cluster to the extended $\{Mo_{63}\}$ -type on capping with six MoO^{4+} groups,^[18] from the Mo_{176}^{6-} to the Mo_{248} -type cluster anion on capping with two neutral $\{Mo_{36}\}$ fragments.^[19] A further example refers to remarkable processes occurring during the formation of the unsymmetrical molybdenum oxide based $\{Mo_{37}\}$ cluster: after a highly reduced ϵ -Keggin-type $\{Mo^V_{12}\}$ unit is capped by four electrophilic MoO_3 groups, which are then reduced, the resulting species is capped by the positively charged $\{Mo_{11}\}$ and $\{Mo_{10}\}$ fragments. (In many cases these types of processes cause a decrease of unusual very large negative charges of the intermediates.)^[18]
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- [29] I. Hargittai, M. Hargittai, *Symmetry through the Eyes of a Chemist*, VCH, Weinheim, **1986**; P. Curie, *J. Phys. (Paris)* **1894**, *3*, 393; see also: I. Hargittai, M. Hargittai, *In Our Own Image: Personal Symmetry in Discovery*, Kluwer, New York, **2000**, p. 216.
- [30] It seems reasonable to assume that during the route to **1a** an anion with the approximate shape of B is first formed, which is—because of its much larger hydrophilic surface—more soluble than **1a**.
- [31] H. S. M. Coxeter, *Introduction to Geometry*, Wiley, New York, **1989**, pp. 152–154.
- [32] See ref. [31], pp. 373–374.
- [33] Given a vertex v in a polyhedral net incident with k distinct polygons, one n_1 -, one n_2 -, ..., and one n_k -gon, its combinatorial curvature is $2 - (n_1 - 2)/n_1 + (n_2 - 2)/n_2 + \dots + (n_k - 2)/n_k$ if that vertex is an interior vertex, and $1 - (n_1 - 2)/n_1 + (n_2 - 2)/n_2 + \dots + (n_k - 2)/n_k$ if it lies on the boundary. If the combinatorial curvature at a vertex v is positive (negative), so is the expected geometric curvature at that vertex for any “reasonable” embedding of the polyhedron in 3-space (e.g. the combinatorial curvature at each of the 60 vertices of the spherically shaped C_{60} polyhedron is easily computed as $2 - (4/6 + 4/6 + 3/5) = 1/15$). Euler’s theorem can be rephrased in terms of combinatorial curvatures as stating that their sum, taken over all vertices of a given polyhedron P, is—quite independently of that polyhedron’s specific structure—always equal to four if the polyhedron’s topology is that of a sphere (e.g. the combinatorial curvature at each vertex of a 60-vertex polyhedron of spherical shape must be $1/15$ in the average, and it must be equal to $1/15$ whenever all vertices have the same combinatorial curvature) and that it vanishes whenever the polyhedron’s shape is that of a torus or that of a cylinder, i.e. a body shaped like an open tube with two circular boundary lines while this sum is negative for every polyhedron of higher genus. This implies that every region of a polyhedral net with predominantly positive combinatorial curvature must have the shape of a cap while an area of predominantly negative combinatorial curvature must be saddle shaped. A case in point are Fowler’s Phantasmagorical Fulleroids (see “Phantasmagorical Fulleroids”: A. Dress, G. Brinkmann, *Match* **1996**, *33*, 87–100), the two smallest possible fulleroidal structures with icosahedral symmetry consisting of pentagons and heptagons, only, as depicted in Figure 6a. They illustrate negative curvature inbetween the areas with strong positive curvature. See also [31] for background material and further details.
- [34] Note that the sum $240 \times (4/315) + 48 \times (4/315) - 16 \times (30/315) - 24 \times (28/315)$ vanishes as predicted by Euler’s theorem.

Ligand-Templated Four-Metal Chains Dimerize into a Unique $[\text{Cu}_8]$ Cluster**

Guillem Aromí, Patrick Gamez, Olivier Roubeau, Huub Kooijman, Anthony L. Spek, Willem L. Driessen, and Jan Reedijk*

Within the context of what has been termed coordination supramolecular chemistry, remarkable progress has been made in the design and preparation of multidentate ligands capable of participating in complicated molecular structures upon complexation, in predetermined manners, with transition metals.^[1] This approach is starting to take hold in the area of molecular magnetism. Thus, in recent years, a few important reports have appeared describing the formation of new magnetic transition metal clusters through the template action of specifically designed multinucleating ligands.^[2] We have reported the synthesis of an O-pentadentate donor possessing a phenol and two β -diketone units (H_3L), which was conceived to direct the formation of chains



of closely spaced transition metals.^[3] Initial efforts into the investigation of its coordination properties involved reactions with Mn^{II} ions, and led to the preparation of a trinuclear complex with formula $[\text{Mn}_3(\text{HL})_3]$ which displayed an asymmetric array of metals.^[4] A significant step forward in the exploration of the templating capability of this new ligand is reported here with the fascinating methoxide-mediated aggregation of two ligand-templated $[\text{Cu}_4]$ chains into an entirely new octanuclear Cu^{II} cluster held together by a fully deprotonated form of H_3L .

The title compound was prepared by treating a methanolic solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ with a solution containing 0.125 equivalents of H_3L and 1.8 equivalents of NtBu_4OH in MeOH. The green powder that precipitated was recrystallized from MeOH/ Et_2O to yield green crystals of $[\{\text{Cu}_4(\text{L})(\text{OMe})_4(\text{NO}_3)_2\}]_2$ (**1**)^[5] in an overall yield of 21 %. The organic salt is introduced into the reaction mixture as the base necessary to deprotonate H_3L and also as the acceptor of the protons from

methanol to give the MeO^- ions that become incorporated into the complex. The fact that the complex binds methoxide instead of hydroxide ions despite the larger Brønsted basicity of the former can be explained by the stability of the final product combined with the large excess of methanol present in the system. The latter point is supported by the observation that, upon prolonged exposure to air, complex **1** changes color from green to brown, presumably following a process of complete hydrolysis of the methoxide ligands, as suggested by elemental analysis.^[6]

The structure of **1**^[7] (Figure 1) shows a unique $[\text{Cu}_8]$ cluster formed by the dimerization of two ligand-held four-metal atom rows. Both metallic chains are bound to each other through eight methoxide ligands: six in a triply bridging

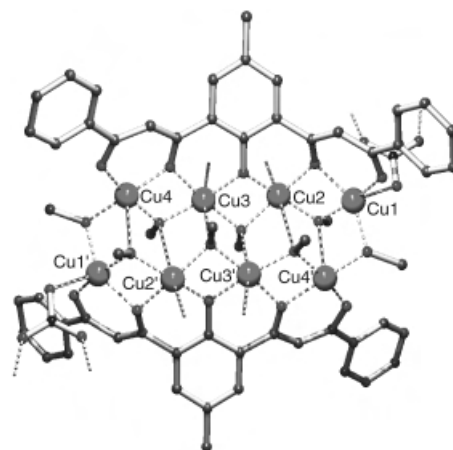


Figure 1. POV-Ray representation of $[\{\text{Cu}_4(\text{L})(\text{OMe})_4(\text{NO}_3)_2\}]_2$ (**1**), where the axial bonds around the Cu^{II} ions are highlighted by striped lines.

manner^[8] and two in a $\mu\text{-OMe}^-$ fashion. The coordination around the Cu centers is completed by nitrate ions, which connect, in an extremely unusual $\eta^3\text{-}\mu_3\text{-NO}_3^-$ mode,^[9] the $[\text{Cu}_8]$ units into one-dimensional polymeric chains of clusters parallel to the a -axis (Figure 2). In fact, this compound represents a new and important addition to the small family of Cu-cluster polymers.^[9–10] The octanuclear cluster possesses a crystallographic center of symmetry which relates one of the $\{\text{Cu}_4(\text{L})(\text{OMe})_4(\text{NO}_3)\}$ units to the other. The core of complex

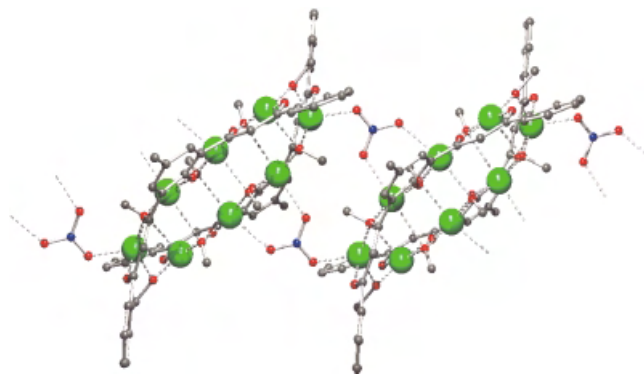


Figure 2. POV-Ray representation of **1** emphasizing the polymerization of $[\text{Cu}_8]$ clusters in the solid state through $\eta^3\text{-}\mu_3\text{-NO}_3$ bridges. Green: Cu, red: O, blue: N, gray: C.

[*] Prof. Dr. J. Reedijk, Dr. G. Aromí, Dr. P. Gamez, O. Roubeau, Dr. W. L. Driessen
Leiden Institute of Chemistry
Gorlaeus Laboratories, Leiden University
PO Box 9502, 2300 RA Leiden (The Netherlands)
Fax: (+31) 71-527-4671
E-mail: reedijk@chem.leidenuniv.nl

Dr. H. Kooijman, Prof. Dr. A. L. Spek
Bijvoet Center for Biomolecular Research
Crystal and Structural Chemistry, Utrecht University
Padualaan 8, 3584 CH Utrecht (The Netherlands)

[**] Financial support by the European Union, under contract HPMF-CT-1999-00113 (Marie Curie Fellowship; G.A.) and TMR ERB-FMNRX-CT98-0199 (O.R.), the NRSC (P.G.), the WFMO (J.R.), and the CW-NWO (A.L.S.) are gratefully acknowledged.

1 (Figure 3) is the first of its kind amongst the family of alkoxide and hydroxide-bridged Cu clusters. The core has been identified, however, as a fragment of a 2D Cu/OH/OAc polymeric structure.^[11] Other large transition metal aggregates, such as the tetraicosanuclear cluster $[\text{Co}_{24}(\text{OH})_{18}(\text{OMe})_2\text{Cl}_6(\text{mhp})_{22}]$ (Hmp = 2-methyl-6-hydroxypyridine),

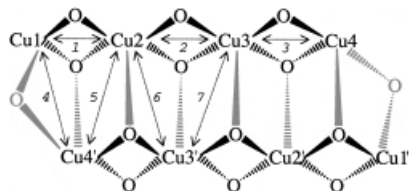


Figure 3. The $[\text{Cu}_8\text{O}_{14}]$ core of **1** showing in gray the Cu–O bonds linking both $[\text{Cu}_4\text{O}_6]$ structural units. The seven unique interactions between adjacent Cu ions necessary to describe the magnetic coupling in **1** are marked with arrows.

include this moiety as part of their structure.^[12] The core of **1** contains two linear rows of four alkoxide-bridged Cu ions, each of which is described as a three-edge-sharing $\{\text{Cu}_2\text{O}_2\}$ unit. Both $[\text{Cu}_4]$ arrays are linked through six axially elongated bonds between the Cu ions and the $\mu_3\text{-OMe}^-$ groups, and two additional $\mu\text{-OMe}^-$ ligands. The Cu...Cu distances within the intrachain $\{\text{Cu}_2\text{O}_2\}$ units are 2.8999(8) (Cu1...Cu2), 2.8834(7) (Cu2...Cu3), and 2.9995(8) Å (Cu3...Cu4). The seven shortest interchain Cu...Cu vectors are described by four values by virtue of the symmetry of the cluster: 2.9610(9) (Cu1...Cu4'), 3.4677(8) (Cu2...Cu4'), 3.3225(8) (Cu2...Cu3'), and 3.2981(8) Å (Cu3...Cu3'). The presence of seven inequivalent, bridged Cu_2 pairs demonstrates the number of exchange parameters necessary for a rigorous description of the magnetic coupling within this cluster (see below). The templating action of the pentadentate ligand L^{3-} undoubtedly plays a crucial role in the formation of this unprecedented topology. The combination of unrestrained β -diketonate ligands and alkoxide groups has been reported to yield more-extended aggregates rather than linear arrangements.^[13] The five strategically disposed oxygen donor atoms in L^{3-} direct the assembly of four Cu ions into metallic arrays, through the formation of four adjacent six-membered chelate rings. The structural constraints that derive from this assembly result in a marked bending of the ligand along its longest dimension as emphasized in Figure 2, which also translates into a curvature of the $[\text{Cu}_4]$ chain (the Cu1–Cu2–Cu3 and Cu2–Cu3–Cu4 angles are $159.78(2)^\circ$ and $170.18(3)^\circ$, respectively). The four unique metal ions are accommodated within the structure of this cluster in three common geometric environments for Cu^{II} ions, namely, tetragonally elongated octahedral (Cu2 and Cu3), intermediate between square pyramidal and trigonal bipyramidal (Cu1, with $\tau=0.50$),^[14] and square pyramidal (Cu4, with $\tau=0.01$). The axial positions of these ions correspond to the six long bonds connecting the $[\text{Cu}_4]$ chains through $\mu_3\text{-OMe}^-$ ligands, or are occupied by oxygen atoms from the nitrate groups (see Figure 1). The remaining Cu–O bonds lay in equatorial positions. All the bond lengths fall within the ranges usually observed for

the coordination of oxygen to Cu^{II} ions in such environments.^[15]

Variable-temperature magnetic susceptibility measurements were performed over the 2–300 K range on a polycrystalline sample of **1** protected from air and under a constant magnetic field of 1 kG. A plot of the magnetic susceptibility (χ_m) per $[\text{Cu}_8]$ cluster, versus temperature T (Figure 4) shows a broad maximum at about 180 K. This

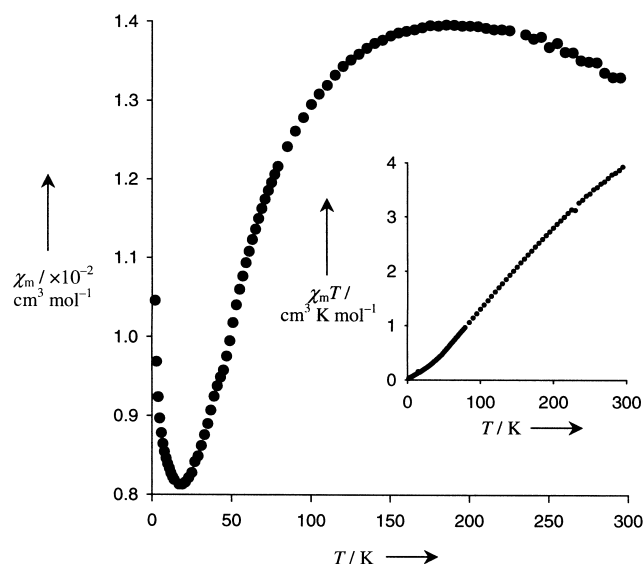


Figure 4. Plot of the magnetic susceptibility (χ_m) versus T for **1**. The inset shows a plot of $\chi_m T$ versus T of **1** over the same temperature range.

feature indicates that the magnetic exchange in this temperature interval is mainly influenced by antiferromagnetic interactions, and leads to a total spin ground state of $S_T=0$. The small increase in the χ_m value below 19 K is typical for the presence of a small amount of paramagnetic impurity, which is very common in such systems.^[16] A regime of uncoupled spins has not yet been reached at the highest measured temperature. This is clear from the plot of $\chi_m T$ versus T (Figure 4, inset), which does not show saturation at 300 K. The value of $\chi_m T$ at room temperature (4.09) is higher than that expected for eight uncoupled Cu^{II} ions with $g=2$ (3.00).

A full investigation over a larger temperature range is under way to obtain a detailed description of the magnetic properties of **1**. An important point to elucidate is whether the high value of $\chi_m T$ at 300 K arises from the presence of strong ferromagnetic interactions in the cluster. The symmetry of this system shows that it is necessary to define seven independent coupling constants for the description of its magnetic exchange (Figure 3). This scheme does not allow for the application of the Kambe vector coupling method^[17] to obtain the energy of its various spin states. Thus, a full-matrix diagonalization method will be necessary for a quantitative treatment. In addition, the possibility of nitrate-mediated intercluster interactions will need to be considered.

The potential of L^{3-} to assemble transition metals into unprecedented, magnetically coupled building blocks for the construction of new clusters has been demonstrated with complex **1**, and is currently being investigated with other

3d elements under a variety of conditions. The prospect of the preparation of mixed-metal moieties is also being explored.

Received: October 10, 2001

Revised: December 12, 2001 [Z18040]

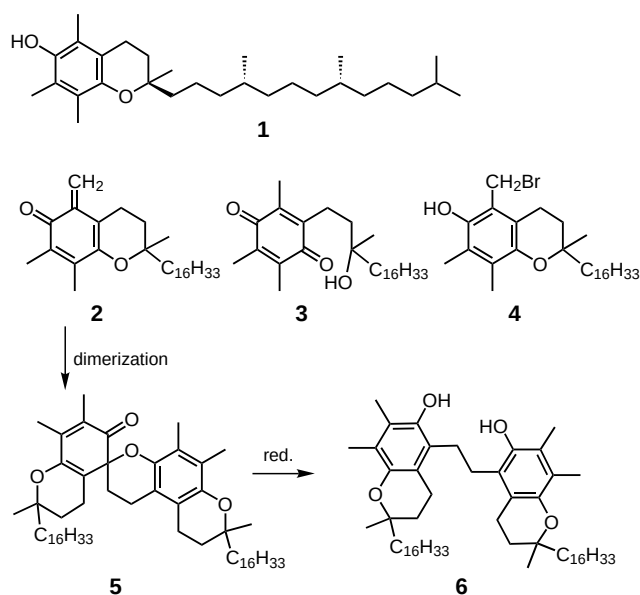
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- [5] Elemental analysis calcd for **1** · MeOH: C 41.50, H 3.66, N 1.64; found: C 41.11, H 3.30, N 1.75.
- [6] Elemental analysis of **1** after hydrolysis calcd for $[\text{Cu}_4(\text{L})(\text{OH})_4(\text{NO}_3)_2] \cdot 2.8\text{H}_2\text{O}$: C 36.09, H 3.22, N 1.68; found: C 35.82, H 2.87, N 1.69.
- [7] Crystal data for **1**: $\text{C}_{29}\text{H}_{29}\text{Cu}_4\text{NO}_{12}$ · solvent (see below). Data were collected on a green block-shaped crystal ($0.2 \times 0.2 \times 0.3$ mm), triclinic, space group $P\bar{1}$ (no. 2) with $a = 10.5682(15)$, $b = 13.510(2)$, $c = 13.9695(14)$ Å, $\alpha = 100.964(9)^\circ$, $\beta = 98.654(10)^\circ$, $\gamma = 96.257(12)^\circ$, $V = 1916.3(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.452$ g cm⁻³, $\mu(\text{MoK}\alpha) = 2.24$ mm⁻¹. 30251 Reflections were measured, 6936 of which were independent ($R_{\text{int}} = 0.0600$, $R_\sigma = 0.0359$, no absorption correction applied) on a Nonius KappaCCD diffractometer with a rotating anode ($T = 150$ K, $1.6 < \theta < 25.25^\circ$, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å). The structure was solved by automated direct methods (SHELXS86), and refined on F^2 (SHELXS-97). The structure contains two sets of interconnecting channels that run in directions [100] and [101] that are filled with a mixture of disordered MeOH and Et₂O molecules. The electron density (240 e in 524 Å³ for each unit cell) was taken into account in the refinement by PLATON/SQUEEZE. Where relevant, data cited above are given without disordered solvent contributions. One of the phenyl rings (C151–C156) is refined with a two-site disorder model. Hydrogen atoms were included on calculated positions riding on their carrier atoms. Refinement of 406 parameters converged at a final $wR2$ value of 0.1031, $R1 = 0.0403$ (for 6309 reflections with $I > 2\sigma(I)$) $S = 1.044$, $-0.86 < \Delta\rho < 2.09$ e Å⁻³. CCDC-171479 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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- [15] Axial Cu–O bond lengths: a) to μ_3 -OMe: 2.743(3) (Cu2), 2.389(3) (Cu3), and 2.418(3) Å (Cu4) and b) to μ_3 -NO₃: 2.226(3) (Cu1), 2.340(3) (Cu2), and 2.433(3) Å (Cu3). Equatorial Cu–O bond lengths: a) to μ -O(ligand): 1.906(3)–1.994(3) Å, b) to μ -OMe: 1.958(3) (Cu1) and 1.921(3) (Cu4), and c) to μ_3 -OMe: 1.935(2)–1.954(3) Å.
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Calixarene-Type Macrocycles by Oxidation of Phenols Related to Vitamin E**

Thomas Rosenau, Antje Potthast, Andreas Hofinger, and Paul Kosma*

α -Tocopherol (**1**), the major component of vitamin E, is the biologically most active lipid-soluble phenolic antioxidant in mammalian tissues.^[1] The two main reactions of vitamin E in vivo are formation of the relatively stable α -tocopheroxyl radical and its bimolecular self-reaction to give free α -tocopherol and *ortho*-quinone methide (*o*-QM) **2**. The latter reaction involves selective transfer of a H atom from the 5-methyl group^[2] of one radical to the phenoxyl oxygen atom of the other radical.^[3] The extremely high antioxidant behavior of α -tocopherol^[4] has been attributed to the geometry of the pyran ring, which allows for optimum spin delocalization.^[5]

With the “siamese twin” model compound **8**, which was obtained in good yield (76 %) by condensation of trimethylhydroquinone (**7**) with 1,1,3,3-tetramethoxypropane (Scheme 1),^[6] it became possible for the first time to “lock” the alicyclic chromane ring into a specific geometry (without disturbing the characteristic vitamin E structure by the introduction of large substituents). Any conformational change in one of the two chromanol moieties in **8**, which would influence the radical stability,^[5] is accompanied by the reverse change in the second chromanol moiety, thus causing



Scheme 1. Structure of α -tocopherol (vitamin E) and some of its characteristic reaction products.

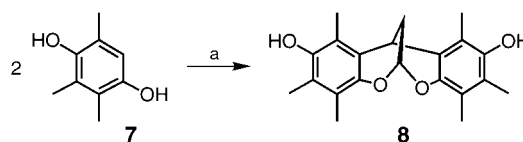
[*] Prof. Dr. P. Kosma, Dr. T. Rosenau, Dr. A. Potthast, Dr. A. Hofinger
Institut für Chemie
Universität für Bodenkultur
Muthgasse 18, 1190 Vienna (Austria)
Fax: (+43) 1-36006-6071
E-mail: pkosma@edv2.boku.ac.at

[**] This work was supported by the FWF (grant no. P14687).

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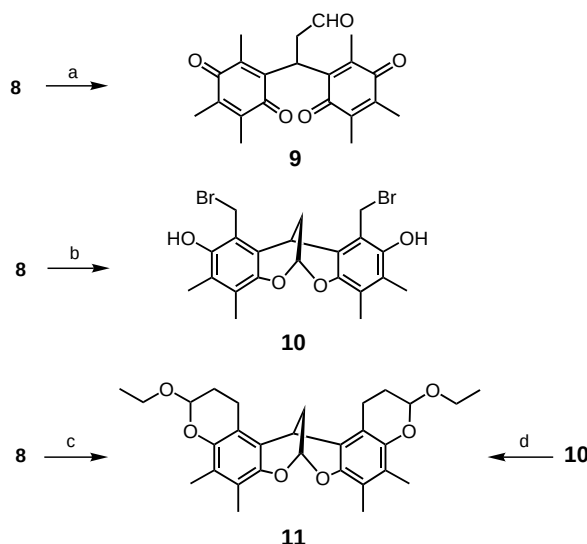
the opposite effect there. Computational results predict the formation of stable mono- and biradicals from **8** and a spin delocalization over both phenolic rings, despite the presence of a nonconjugated spacer. Preliminary EPR experiments have shown 7-line spectra ($g = 2.0048 \pm 0.0002$) resembling those of α -tocopherol, but exhibiting additional hyperfine structure.

From the viewpoint of the chemical behavior, it could reasonably be expected that all the characteristic reactions of vitamin E (Scheme 2) would occur twice in **8**. Oxidation of α -tocopherol (**1**) with FeCl₃ in aqueous methanol is known to



Scheme 2. a) (MeO)₂CHCH₂CH(OMe)₂, CHCl₃/CF₃COOH (2/1), N₂, 24 h, 76 %.

afford the corresponding *p*-quinone.^[7] Model compound **8** showed analogous oxidation behavior, and a bis(*p*-quinone) **9** (Scheme 3) was obtained. Bromination, which produces



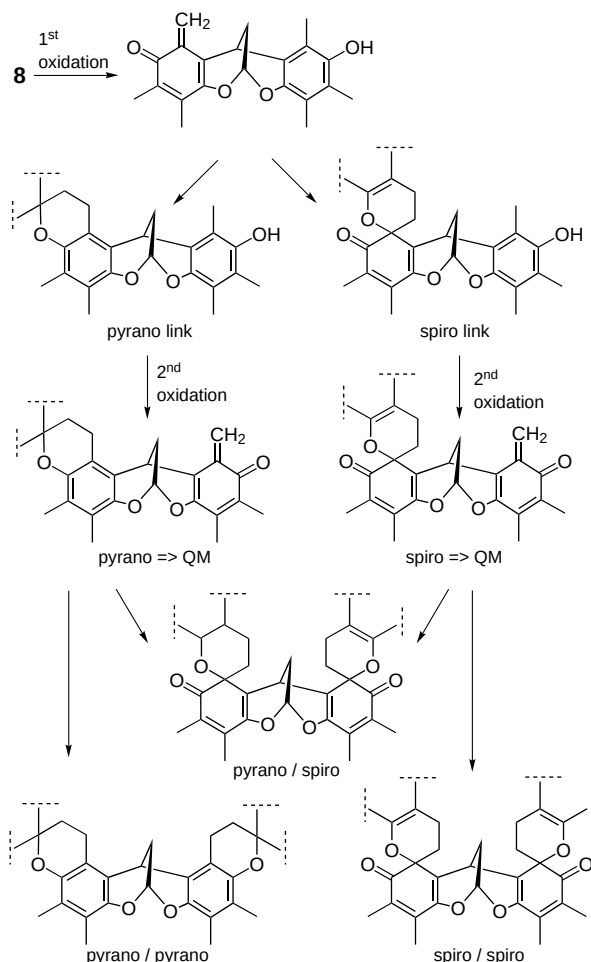
Scheme 3. a) FeCl₃ or AgNO₃, MeOH/H₂O (5/1), 1 h, reflux, 84–86 %; b) Br₂, *n*-hexane, 2 h, 100 %; c) Ag₂O, CH₂=CHOEt, *n*-hexane, 4 h, reflux, 23 %; d) CH₂=CHOEt, Ag₂O or NEt₃, CH₂Cl₂, –10 °C, 2 h, 86 %.

tocopheryl bromide **4** from α -tocopherol,^[8] also proceeded twice in molecule **8** to afford dibromide **10**. Only dibrominated product **10** and unchanged starting material was found (but no monobromination product was formed) when substoichiometric amounts of Br₂ at –78 °C were used. Bromination of the first chromanol part thus favors reaction of its “twin”.

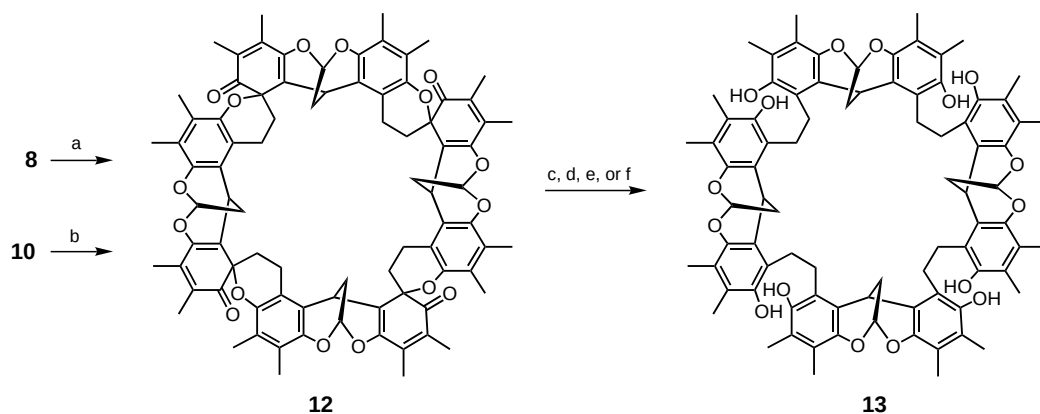
The involvement of *o*-QM structures in the chemistry of **8** was demonstrated by trapping these intermediates with ethyl vinyl ether in a hetero-Diels–Alder reaction with inverse electron demand (Scheme 3). The oxidation of **8** with Ag₂O in non-aqueous media or treatment of dibromide **10** with bases

afforded the same trapping product **11**. Again, only the symmetric structure was obtained; reaction of only one “half” of the molecule was not observed.

Both of the two chromanol units in **8** could be expected to undergo a reaction similar to the dimerization of tocopherol to form a spiro compound (Scheme 4).^[9] After reaction of the



Scheme 4. Formation of pyrano/spiro, pyrano/pyrano, and spiro/spiro bridges by reaction of **8** as diene/dienophile, diene/diene, or dienophile/dienophile, respectively.



Scheme 5. a) Ag₂O, *n*-hexane, 96 h, 27%; b) morpholine, CH₂Cl₂, -78 °C, 1 h, 72%; c) ascorbic acid, MeOH/H₂O, 48 h, RT, 74%; d) NaBH₄, *i*PrOH, 3 h, RT, 26%; e) Zn, HCl (1M), MeOH, 3 h, RT, 93%; f) **8**, PhMe, reflux, 6 h, 8%.

first chromanol unit of **8**, for example, as a dienophile, the second half can react either as a dienophile or as a diene. Compound **8** would thereby be converted into a pyrano/spiro, a pyrano/pyrano, or a spiro/spiro couple. The second side of the two molecules of **8** attached to the first twin pair has again two options in reacting further, and so on. Thus, the same process that causes a dimerization of α -tocopherol to spiro compound **5** would result in a rather irregular oligomerization in the case of model compound **8**. In the materials produced in the latter case, the “monomeric” C₂₁H₂₀O₄ units are connected through spiro links, formed in sequential hetero-Diels–Alder reactions.

The reaction of *o*-QM precursors in refluxing toluene indeed afforded the expected complex oligomer mixtures: oxidation of **8** with Ag₂O gives tetramers ($M = 1349.5 \text{ g mol}^{-1}$) up to octadecamers ($M = 6058.7 \text{ g mol}^{-1}$), while dehydrobromination of **10** gave hexamers up to nonamers, with both oligomer “ends” still substituted with Br atoms. The generation of *o*-QM at room temperature afforded one major product together with smaller amounts of oligomers (up to the pentamer). At -78 °C, however, a single product was obtained in good yield (72 %): the cyclic tetramer **12** ($M = 1345.6 \text{ g mol}^{-1}$), which contained exclusively pyrano/spiro (=spiro/pyrano) pairs, but no pyrano/pyrano or spiro/spiro couples, as the building blocks (Scheme 5).^[10]

The selective formation of a pyrano moiety on the opposite side of a spiro structure (and vice versa) can be rationalized in terms of frontier orbital theory. The observed selectivity in the oligomerization is indicative of an electronic effect of the first link in the oxidized **8** on the *o*-QM unit located in the other half of **8**. Computational results^[11] showed that reaction of the first twin in **8** as a diene (pyrano structure) results in an increase in the HOMO energy of the *o*-QM unit in the other half of the molecule by 0.25 eV. Therefore, the presence of a pyrano structure on one side increases the π -donor ability, and the *o*-QM unit on the other side will react as a dienophile, and thus form a spiro structure; thus, this reaction sequence results in a pyrano/spiro pair. By analogy, reaction of the first twin in **8** as a dienophile (spiro structure) decreases the LUMO energy of the *o*-QM on the opposite side by 0.21 eV, which leads to increased π -acceptor capability and subsequent reaction as a diene (pyrano structure) to form a spiro/pyrano

couple. Thus, a molecule **8** which has reacted as a diene on one side will react as dienophile on the other side, and vice versa, as a result of the significantly decreased HOMO–LUMO energy difference for these asymmetric pairs compared to the symmetric couples. Hence, pyrano/spiro (spiro/pyrano) pairs are formed exclusively.

The tetramer **12** bears not only structural resemblance to spiro compound **5**, but also exhibits surprisingly similar chemical behavior. Analogous to **5**, whose most important reaction is the reduction to the ethano-dimer **6** by the mild reductant ascorbic acid,^[12] tetramer **12** was also reduced to the tetra-ethano derivative **13** (Scheme 5). Even though **13** contains tetracycles tethered by ethylene bridges, its structural appearance as well as solubility and analytical properties are quite close to those of calixarenes (Figure 1), which consist of monocyclic phenolic units linked by methylene groups. The formation of an inclusion complex was observed for **13** with, for example, *o*-PhCl₂ or anthracene.^[13] The use of these aromatic guests also allows the study of the complexing properties of the novel macrocycles by UV and fluorescence spectroscopy.

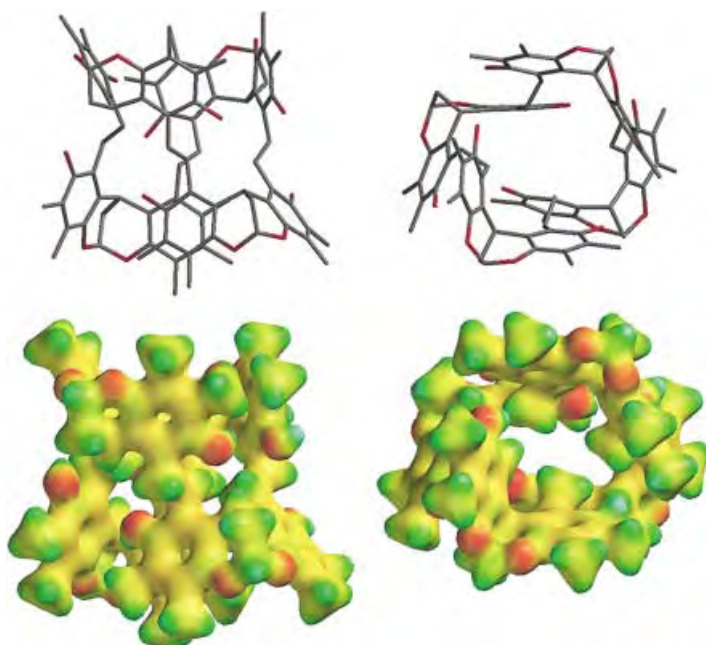


Figure 1. Energy-minimized structure of **13** with a calixarene-type 1,3-alternate conformation, based on computational results; hydrogen atoms in the top structures have been removed.

In conclusion, model compound **8** allows for deeper insights into the reactivity of tocopherols and tocopheroxyl radicals. In addition, the presented facile tertiary sequence of oxidation, multiple hetero-Diels–Alder reactions, and reduction provides an easy access to novel, complex calixarene-type macrocycles.

Experimental Section

8: White needles; m.p. 225–228 °C; ¹³C NMR (75.47 MHz, [D₆]DMSO): δ = 12.9, 13.5 (^{7a}CH₃, ^{8b}CH₃), 14.5 (^{5a}C), 26.1 (⁴C), 28.5 (³C), 91.2 (²C), 120.4 (¹C), 121.4 (⁸C), 123.1 (^{4a}C), 123.9 (⁷C), 143.9 (^{8a}C), 147.3 (⁶C); IR (KBr): $\tilde{\nu}$ = 3452

(br, OH), 2952 and 2870 (CH₃), 1639 (aromatic ring), 1080, 1209 cm⁻¹ (^{Ar}C–O–C); elemental analysis calcd for C₂₁H₂₄O₄ (340.40): C 74.09, H 7.11; found: C 73.97, H 7.24.

13: White powder; m.p. > 350 °C; ¹³C NMR (75.47 MHz, [D₆]DMSO, 90 °C): δ = 12.1 (^{7a}CH₃), 12.6 (^{8b}CH₃), 18.5 (⁴CH), 27.6 (³CH₂), 32.1 (^{5a}CH₂), 90.4 (O–CH₂–O), 119.5 (⁵C), 120.6 (⁸C), 122.2 (^{4a}C), 123.0 (⁷C), 143.0 (^{8a}C), 146.4 (⁶C); IR (KBr): $\tilde{\nu}$ = 3474 (br, OH), 2956, 2865 (CH₃), 1597 (aromatic ring), 1076, 1211 cm⁻¹ (^{Ar}C–O–C); positive-ion MALDI-TOF MS: *m/z* calcd for C₈₄H₈₇O₁₆Na [*M* – H + Na]⁺: 1375.51, found: 1375.62; elemental analysis calcd for C₈₄H₈₈O₁₆ (1353.63): C 74.54, H 6.55; found: C 74.72, H 6.82.

Received: September 28, 2001 [Z17984]

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Natural Product Derived Receptor Tyrosine Kinase Inhibitors: Identification of IGF1R, Tie-2, and VEGFR-3 Inhibitors**

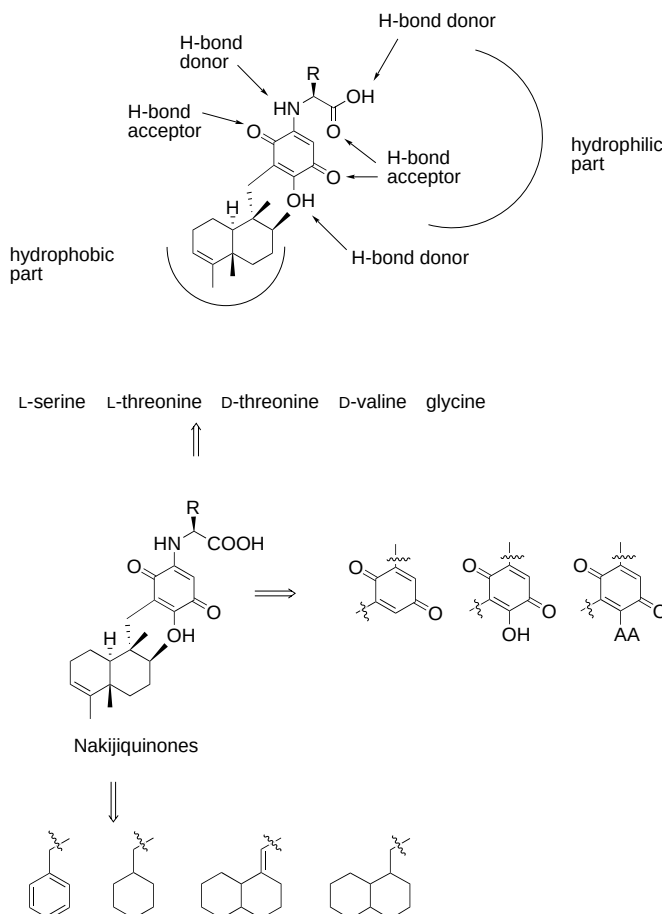
Petra Stahl, Lars Kissau, Ralph Mazitschek, Athanassios Giannis,* and Herbert Waldmann**

Angiogenesis, the development of new blood vessels from pre-existing ones, is central to wound repair, inflammation, and embryonic development. Furthermore, aberrant angiogenesis is considered to be a key step in tumor growth, spread, and metastasis.^[1, 2] Vascular development depends on endothelium-specific receptor tyrosine kinases, in particular the vascular endothelial growth factor receptors 1–3 (VEGFR1–3) and the Tie-2 receptor.^[3] All these receptors have been implicated in tumor angiogenesis,^[4–8] and antagonization of Tie-2, VEGFR-2, or VEGF-D (a ligand of VEGFR-3) inhibits tumor growth and tumor metastasis in vivo.^[7, 9, 10] The development of low molecular weight inhibitors of these receptor tyrosine kinases is among the most promising approaches to the development of new, alternative antitumor drugs, and several inhibitors of VEGFR-2 are in clinical trials.^[11, 12] The combination of VEGFR-2 inhibitors with Tie-2 antagonists should potentiate their anti-angiogenic effects.^[6] Furthermore, inhibitors of VEGFR-3 would suppress the metastasis of lymphogenic tumors. To date however, only a few cases of small-molecule inhibitors of the Tie-2 and VEGFR-3 receptors have been reported.^[13] Herein we describe the identification of inhibitors of these proteins from a compound library that was derived from a natural product.

We have recently proposed a new concept for enhancing the process of finding lead compounds, by use of combinatorial methods.^[14] The key principle of this concept is to employ natural products with known biological activity as biologically validated starting points in structural space, which are selected by evolution for binding to structurally conserved, yet genetically mobile protein domains. The frameworks of such natural products may then serve as a guiding

principle for the development of relatively small compound libraries, which should yield significantly higher hit-rates than much larger libraries, designed exclusively on the basis of available and proven chemical transformations.

In the light of this concept, we synthesized a library of 56 nakijiquinone analogues (Scheme 1), the only natural products known to be inhibitors of the Her-2/Neu receptor tyrosine kinase,^[15] and investigated these analogues as possible inhibitors of the receptor tyrosine kinases involved in angiogenesis.



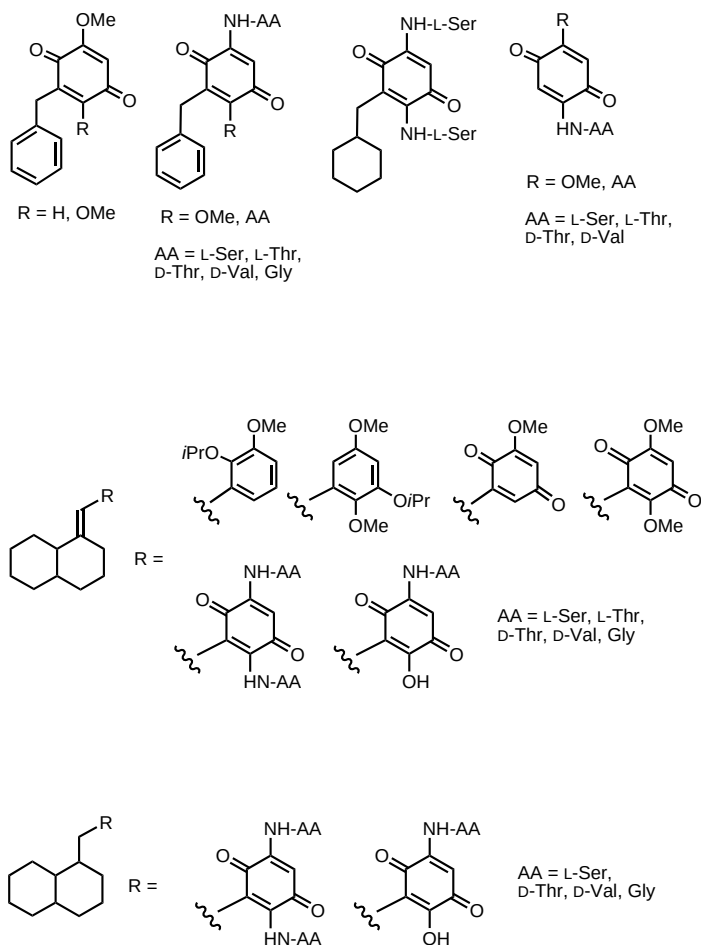
Scheme 1. Structure of the nakijiquinones and plan for the synthesis of nakijiquinone analogues.

The design of the nakijiquinones analogues was based on the modular structure of the natural products. The nakijiquinones consist of a hydrophobic diterpene unit, which may interact with a hydrophobic pocket close to the ATP binding site,^[12] a quinone-type building block, and an amino acid, the latter two of which may participate in hydrogen bonding to the ATP binding site of kinases. Consequently, the diterpene part was replaced with simple hydrophobic structures (Scheme 1). The hydrophilic amino acids serine and threonine, and the hydrophobic acids valine and glycine were chosen, and the stereochemistry was also varied. To modify the type and number of hydrogen-bond donors and acceptors, we introduced either one or two amino acids, an amino acid and an OH group, or only one amino acid.

[*] Prof. Dr. H. Waldmann, Dr. P. Stahl, Dipl.-Chem. L. Kissau
Max-Planck-Institut für molekulare Physiologie
Abteilung Chemische Biologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
Fax: (+49) 231-133-2499
and
Universität Dortmund, Fachbereich 3
Organische Chemie, 44221 Dortmund (Germany)
E-mail: herbert.waldmann@mpi-dortmund.mpg.de
Prof. Dr. A. Giannis, Dipl.-Chem. R. Mazitschek
Institut für Organische Chemie
Universität Karlsruhe
Richard-Willstätter-Allee 2, 76128 Karlsruhe (Germany)
Fax: (+49) 721-608-7652
E-mail: giannis@ochhades.chemie.uni-karlsruhe.de

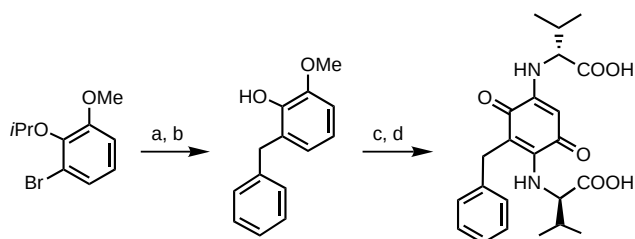
[**] This research was supported by the Fonds der Chemische Industrie. R.M. is grateful to the State of Baden-Württemberg for a scholarship from the Landesgraduiertenförderung. L.K. is grateful to the Studienstiftung des deutschen Volkes and the Fonds der Chemische Industrie for scholarships; IGF1R = insulin-like growth factor 1 receptor, Tie-2 = tyrosine kinase with immunoglobulin and epidermal growth factor homology domains, also called Tek, VEGFR-3 = vascular endothelial growth factor receptor 3.

Scheme 2 shows the majority of the library members that were synthesized. A series of analogues was built up, in which the diterpene unit was replaced either by a benzyl group, a cyclohexane ring, a *n*-butyl group (structure not shown), or by



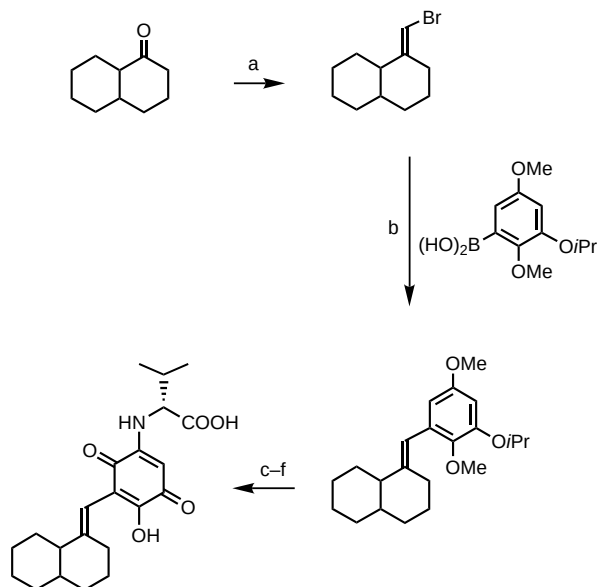
Scheme 2. Representative members of the nakijiquinone library.

a hydrogen atom. In general, these compounds were synthesized from appropriately substituted and selectively protected phenolic ethers, by means of a reaction sequence consisting of selective deprotection, oxidation to the quinoid system, and addition of an amino acid to the resulting vinylogous esters (by analogy to the methods described in the total synthesis of the nakijiquinones; a representative example is given in Scheme 3).^[15]



Scheme 3. Synthesis of an amino acid substituted quinone. a) *n*BuLi, THF, -78°C , 30 min, then CuI $\rightarrow 40^{\circ}\text{C}$; -78°C , benzyl bromide, THF, 55%; b) BCl_3 , CH_2Cl_2 , 0°C , 88%; c) O_2 , $\text{N,N}'$ -ethylenebis(salicylideneiminato)-cobalt(III) (salcomine), DMF, 70%; d) D-valine, NaHCO_3 , EtOH, 75%.

The same aromatic building blocks and the oxygenation/amino acid introduction methodology were employed in the synthesis of analogues with a decalin system. Linkage to a *trans*-decalin building block with an exocyclic double bond was achieved by the Suzuki coupling of substituted arylboronic acids to the corresponding decalin-derived vinyl bromide (a representative example is given in Scheme 4). Reduction of the double bond in the Suzuki products yielded analogues with an alkyl side chain attached to the decalin core.



Scheme 4. Synthesis of a decalin analogue of the nakijiquinones. a) $\text{BrCH}_2\text{PPh}_3\text{Br}$, KOtBu, THF, $-78^{\circ}\text{C} \rightarrow \text{RT}$, 63%; b) $[\text{Pd}(\text{PPh}_3)_4]$, toluene, EtOH, Na_2CO_3 , 90°C , 24 h, 74%; c) BCl_3 , CH_2Cl_2 , 0°C , 89%; d) $\text{ON}(\text{SO}_3\text{K})_2$, H_2O , benzene, aliquat 336, Na_2CO_3 , 78%; e) KOH, MeOH, H_2O , 59%; f) D-valine, NaHCO_3 , EtOH, 56%.

These syntheses gave access to a compound library with 56 members, which was screened for possible inhibitors against receptor tyrosine kinases, selected to cover a wide spectrum of biological activities.

To this end, in addition to VEGFR-2 (KDR, flk-1), VEGFR-3 (flt-4), and Tie-2, Her-2/Neu, epidermal growth factor receptor (EGFR; ErbB-1), ErbB-2, and insulin-like growth factor 1 receptor (IGF1R) were also chosen. The Her-2/Neu proto-oncogene belongs to the EGF family of receptor tyrosine kinases. It is over-expressed in approximately 30% of all primary breast, ovary, and stomach cancers.^[16] The EGFR, which is closely related to Her-2/Neu, has been implicated in human tumorigenesis, for example, of glioblastoma as well as in numerous tumors of epithelial origin including breast and oesophageal tumors.^[17] The insulin-like growth factor 1 receptor affects cell mitogenesis, survival, transformation, and insulin-like activities by the binding of its ligands, IGF1 and IGF2. This receptor influences post natal growth physiology, and its activity has been associated with malignant disorders such as breast cancer.^[18] The anti-apoptotic effect induced by the IGF1/IGF1R system correlates to the induction of chemoresistance in various tumors.^[19]

Out of the 56 compounds subjected to the kinase assay, five compounds displayed inhibitory activity in the low micromolar range. The library of the nakijiquinone analogues did not contain any inhibitor of Her-2/Neu, EGFR, ErbB-2, or VEGFR-2 which warranted further investigation. Remarkably, four of the compounds investigated turned out to be inhibitors of the Tie-2 receptor (Table 1). Two of these (entries 1 and 2) proved to be selective for this kinase; the other kinases in the assay were not significantly inhibited at concentrations of up to 70 μM . In the light of these findings, 14 close analogues of the nakijiquinones, as well as synthetic nakijiquinones A, C, and D,^[15] were investigated as inhibitors of the kinases described above; however, no further inhibitor was found.

The most potent inhibitor identified in this study is bisthreonine derivative **3** (entry 3), which not only inhibits the Tie-2 receptor with an IC_{50} value of 5 μM , but also demonstrates a similar activity against VEGFR-3. These results indicate that **3** may be of interest in the inhibition of angiogenesis in general, and in the prevention of lymphangiogenesis in particular. Furthermore, the functionalization of the central six-membered ring with two amino acid residues suggests that improvements in activity and selectivity may be possible by variation of the amino acid residues.

The data given in Table 1 indicate that a quinoid system flanked by a hydrophobic group (entries 1 and 2) may be important for binding. Thus, the corresponding quinoid compound, analogous to **1** and **2** but lacking a further hydrophobic substituent, inhibits neither Tie-2 nor VEGFR-3. The presence of an amino acid as a vinylogous amide seems to enhance inhibitory activity, probably by providing a hydrogen-bond donor/hydrogen-bond acceptor motif. Notably, compound **4** inhibits the IGF1 receptor selectively with an IC_{50} value of 500 nM. The finding that this small nakijiquinone-analogue library yielded two IGF1R inhibitors indicates that this class of compounds in general may provide a suitable

lead structure for the development of more potent IGF1R inhibitors.

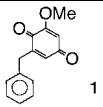
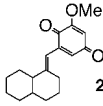
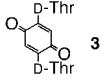
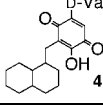
Detailed analysis of the inhibitory activity of **3** revealed that it is a competitive inhibitor and competes with ATP for the binding site of the nucleotide triphosphate. The K_i value and K_M values were found to be 3 μM and 19 μM , respectively (with ATP as the substrate).

To rationalize the selectivity displayed, for example, by compound **4**, which embodies a quinoid system and a hydrophobic annelated ring system and thereby closely resembles the nakijiquinones, the potential binding modes to Tie-2 were investigated by means of molecular modeling experiments. To this end, homology models were constructed for VEGFR-2, VEGFR-3, and Tie-2, which used the available crystal structures of FGFR-1 as templates (Figure 1).^[12, 14, 20] Although an X-ray crystal structure of Tie-2 (apo-enzyme) has been reported,^[21] it does not provide a suitable basis for modeling experiments as receptor tyrosine kinases are known to undergo significant conformational changes upon ligand binding.

The homology models of the Tie-2, VEGFR-2, and VEGFR-3 kinase domains were constructed by using CHARMM,^[22] MODELLER,^[23] WHATCHECK,^[24] and WitolP,^[25] and employed the available crystal structures of the FGF receptor 1 as templates. The crystal structures of the FGF receptor 1 were chosen because of their good sequence agreement within the kinase domain with VEGFR-3 ($\approx 51\%$), Tie-2 ($\approx 45\%$), and VEGFR-2 ($\approx 56\%$). These values are above the 30% minimum, usually considered to be the limit for a good homology model.^[26] The primary alignment was performed by DIALIGN^[27] and corrected manually. For the purpose of building the homology models, the residues of the kinase insert domain were deleted from the sequences.

The choice of orientation of the inhibitors within the ATP binding sites was guided by our previous work^[15] and by the interactions described by Mohammadi et al.^[20] After manual

Table 1. Inhibition of different receptor tyrosine kinases by nakijiquinone analogues.

Entry	Compound	EGFR	IC_{50} for receptor [μM] ^[a] Her-2/Neu	ErbB-2	IGF1R	VEGFR-2	VEGFR-3	Tie-2
1		–	–	–	–	–	–	18
2		–	–	–	–	–	–	14
3		–	–	–	6	–	3	5
4 ^[b]		–	–	–	0.5	–	–	9

[a] To assay the inhibitory activity, the kinase-catalyzed phosphorylation of poly(Glu-Tyr) in the presence of varying concentrations of inhibitor was determined. The kinases were employed as fusion proteins of glutathione-S-transferase (GST) and the respective kinase domain. The relative amount of phosphorylated substrate was quantified by means of an anti-phosphotyrosine enzyme-linked immunosorbent assay (ELISA), which employed an anti-phosphotyrosine antibody conjugated to horseradish peroxidase (POD). The bound antibody was detected by the light emission after addition of a chemiluminescence substrate for POD. [b] Compound **4** was investigated as an inseparable mixture of diastereomers.



Figure 1. Alignment of amino acid sequences of VEGFR-2, VEGFR-3, Tie-2, and FGFR-1. The sequences were obtained from the Swiss-Prot database (VEGFR-2: P35968, VEGFR-3: P35916, Tie-2: Q02763, FGFR-1: P11362).

docking, the energy of the ligand-protein complex was minimized by using CHARMM.^[22] According to these investigations, **4** binds in the mode shown in Figure 2. Compound **4** inhibits Tie-2 in the low micromolar range, but demonstrates

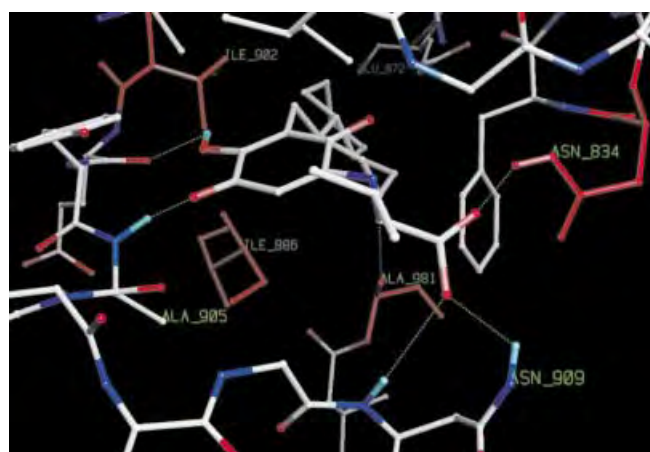


Figure 2. Proposed binding mode of compound **4** to the active site of Tie-2. Side chains that influence selectivity are colored red.

no activity towards VEGFR-2 or VEGFR-3. We attribute this selectivity to unfavorable interactions of the decalin moiety with C989 in VEGFR-2 (corresponds to C900 in VEGFR-3 and A981 in Tie-2) and to the formation of a hydrogen bond between the carboxy group of **4** and the amino acid N834 of Tie-2 (A844 in VEGFR-2 and A855 in VEGFR-3). Compound **4** binds in a manner in which the essential hydrogen bonds to the amino acids E917, C919, and N909 may be formed. Furthermore, amino acids I902 and I886 in Tie-2 cause the hydrophobic pocket in our model to be somewhat smaller than the pockets in VEGFR-2 and VEGFR-3. The decalin moiety of **4** covers the accessible surface in the hydrophobic pocket of Tie-2 much better than in VEGFR-2, where some space is left unoccupied.

We have shown that a relatively small library based on a naturally occurring kinase inhibitor yields potent inhibitors for other kinases with a high hit rate. This led to the identification of IGF1R, Tie-2, and VEGFR-3 inhibitors. These results may open up entirely new opportunities for the suppression of angiogenesis and lymphangiogenesis, and for the development of new anti-cancer drugs. Moreover, the results support our proposed concept for the enhancement of the hit and lead finding process.^[14] The results show that to achieve high hit rates, the synthesis of natural product derived libraries is necessary to counterbalance the varying amino acid sequences found in repeatedly occurring protein domains with similar structures (here the kinase domains). The synthesis of the natural products alone would not have yielded the desired inhibitors.

Received: October 10, 2001 [Z18042]

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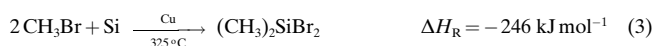
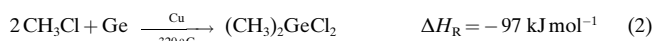
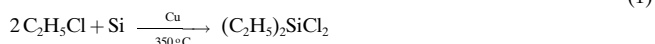
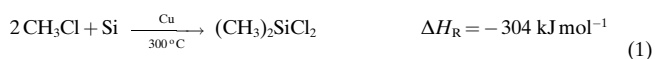
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Selective Direct Synthesis of Organofunctionalized Dialkylgermanes from Solvochemically Activated Germanium**

Sabine Schlecht

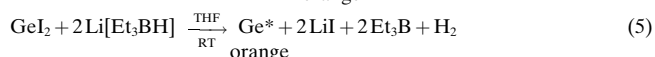
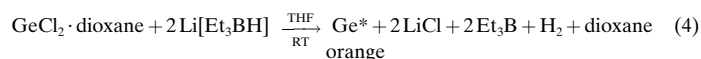
Since the first successful experiments aimed at the direct synthesis of organosilanes and organogermanes, carried out by Rochow and Müller in 1942–1947,^[1, 2] a whole industry for the production and application of alkylchlorosilanes has evolved. The direct synthesis of alkylgermanes, however, has received much less attention, although alkylated polygermylenes^[3] and mixed polygermasilylenes,^[4] the synthesis of which requires diorganogermanium compounds, have gained increasing importance as photoconducting polymers and photoresists. Their surface properties and their absorption maxima depend not only on the type of polymer backbone but also on the nature of the organic substituent on the diorganogermanium compound.^[3, 4]

Like the direct synthesis of alkylchlorosilanes, the oxidative addition of alkyl halides to germanium is also clearly exothermic [Eqs. (1)–(3)].^[5]



Nonetheless, the direct reaction of alkyl halides with elemental silicon or germanium requires very drastic conditions (for the synthesis of an organoelement compound) and the use of a copper catalyst [Eqs. (1)–(3)]. This is due to the pronounced kinetic inertness of the elemental tetrrels. The required reaction temperature of about 300 °C^[5] prevents the use of functionalized organic halides in direct syntheses, because these compounds lack the necessary thermal stability. In the following, the application of solvochemically activated germanium in direct synthesis reactions is reported. When this very reactive form of germanium is used, the oxidative addition takes place at conditions mild enough to allow, for the first time, a direct synthesis of organofunctionalized germanes without the need for a copper-containing additive.

The solvochemical activation of germanium occurs through the reduction of its dichloride with a solution of Li[Et₃BH] in THF^[6] at room temperature [Eqs. (4) and (5)]. Completely X-ray amorphous, orange-colored germanium is obtained under these conditions.



[*] Dr. S. Schlecht
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1, 70569 Stuttgart (Germany)
Fax: (+49) 711-689-1502
E-mail: s.schlecht@kf.mpg.de

[**] This work was supported by a Liebig-Fellowship and a grant from the Fonds der Chemischen Industrie and the BMBF.

This “activated germanium” has been characterized by thermoanalysis, elemental analysis, and IR, Raman, and UV/Vis spectroscopy. The UV/Vis spectrum showed an absorption maximum at $\lambda = 415$ nm. Elemental analysis of the activated germanium revealed the presence of chlorine and hydrogen in the orange solid.^[7] Thus, it can be concluded that the surface is terminated by chloride and hydride. This assumption is strongly supported by the results from vibrational spectroscopy. The Raman spectrum showed a very strong band for the Ge–Ge stretching mode of the amorphous network at 292 cm^{-1} and two weaker bands at 545 cm^{-1} ($\nu(\text{Ge–Cl})$) and 2011 cm^{-1} ($\nu(\text{Ge–H})$). In the IR spectrum two corresponding bands at 550 cm^{-1} ($\nu(\text{Ge–Cl})$) and at 2002 cm^{-1} ($\nu(\text{Ge–H})$) were found. Thermoanalytic investigation of the amorphous germanium showed two distinct signals. At 490°C a signal for an exothermic transition was detected and at 909°C the peak for the endothermic melting process was found. Hence, the melting point of the activated germanium is significantly lowered compared to the one of pure elemental germanium ($T_m = 937^\circ\text{C}$).^[8] Since for films of completely hydrogenated amorphous germanium (a-Ge:H) crystallization temperatures around 430°C have been found,^[9] and the crystallization temperatures of bulk material are expected to be higher than those of films, it is reasonable to assign the exothermic transition at 490°C to the crystallization of the amorphous germanium.^[10]

Clean reaction of the activated germanium with functionalized alkyl bromides can be achieved at $130\text{--}150^\circ\text{C}$, depending on the substrate [Eq. (6)]. Polar substrates with a short hydrocarbon chain react at lower temperatures than nonpolar substrates with longer chains. The reaction times are between 2 and 9 h, depending on the scale of the reaction.



X = CN, COOCH₃, Cl
n = 2–4

The yields of organogermanes vary between 82 and 94%. Unlike industrial direct synthesis, these reactions do not form mixtures of the whole family of organobromogermanes $\text{R}_{4-n}\text{GeBr}_n$, but yield the dialkyl products R_2GeBr_2 with very high selectivity (Table 1). This selectivity for the dialkyl products is maintained at lower reaction temperatures (Table 2), although the lower temperatures no longer allow a complete conversion of the activated germanium, not even

Table 1. Direct syntheses of organofunctionalized germanes from activated germanium Ge*.

Substrate	Product ^[a]	t [h] ^[b]	T [°C]	Yield [%] ^[b]
H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	2	130	82
H ₃ COOCC ₄ H ₈ Br	(H ₃ COOCC ₄ H ₈) ₂ GeBr ₂	2	150	84
NCC ₂ H ₄ Br	(NCC ₂ H ₄) ₂ GeBr ₂	2	130	94
NCC ₃ H ₆ Br	(NCC ₃ H ₆) ₂ GeBr ₂	2	130	85
ClC ₄ H ₈ Br ^[c]	(ClC ₄ H ₈) ₂ GeBr ₂	5	150	84

[a] The corresponding monoalkyl product is either not observed or is found with a yield < 2%. [b] Reaction times and yields for a reaction scale of 1 mmol GeCl₂·dioxane. [c] The substrate was allowed to react in a 50:50 (v/v) mixture with diethyleneglycol dimethyl ether (diglyme).

Table 2. Dependence of the yield and the distribution of products on the reaction temperature in the reaction of activated germanium with BrC₂H₄COOCH₃.

Substrate	Products	T [°C]	t [h] ^[a]	Yield [%] ^[a]
H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	130	2	82
	(H ₃ COOCC ₂ H ₄)GeBr ₃			1–2
H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	120	2	74
	(H ₃ COOCC ₂ H ₄)GeBr ₃			1–2
H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	100	2	34
	(H ₃ COOCC ₂ H ₄)GeBr ₃			0–1

[a] Reaction times and yields for a reaction scale of 1 mmol GeCl₂·dioxane.

at very prolonged reaction times. Yields and distributions of products at different reaction temperatures are given in Table 2 for the reaction of activated germanium with BrC₂H₄COOCH₃.

A variation of the scale of a test system from 1–20 mmol showed that the selectivity found for small-scale reactions is completely preserved in the scale-up (Table 3). Again, the reaction of activated germanium with BrC₂H₄COOCH₃ was chosen as the test system. This system gives the lowest yield and should therefore be the most susceptible to changes in the reaction conditions. The reaction time is prolonged up to 9 h (20 mmol), but no reduction in yield or selectivity has been observed.

Table 3. Dependence of the reaction time on the reaction scale.

Amount of Ge*	Substrate	Products	T [°C]	t [h]	Yield [%]
1 mmol	H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	130	2	82
		(H ₃ COOCC ₂ H ₄)GeBr ₃			1–2
7 mmol	H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	130	6	81
		(H ₃ COOCC ₂ H ₄)GeBr ₃			2
20 mmol	H ₃ COOCC ₂ H ₄ Br	(H ₃ COOCC ₂ H ₄) ₂ GeBr ₂	130	9	83
		(H ₃ COOCC ₂ H ₄)GeBr ₃			1–2

For all reactions described herein it has been indispensable that the residual lithium chloride, which had coprecipitated with the amorphous germanium was washed out thoroughly and completely before the subsequent reaction with an alkyl bromide. Otherwise, the selectivity for the dialkylgermane could not be achieved. The formation of bromogermanes of the type $\text{R}_{(4-(n+m))}\text{GeBr}_n\text{H}_m$ has not been observed for any of the direct syntheses reported here. Organodigermanes or other higher germanes, which are found in the classical Rochow synthesis^[2] as by-products, have not been detected. Criteria for the choice of the different alkyl bromides were a variation of the chain length and an alteration of the functional group. The direct synthesis is of particular synthetic value in the case of functional groups that contain a carbonyl functionality and can therefore not be introduced at the germanium center through the use of Grignard reagents or organolithium compounds. The use of functionalized organozinc compounds such as BrZn(CH₂)_nCOOCH₃,^[11] which are easily accessible, is generally possible here, but would be unfavorable and not competitive with a selective direct synthesis because of the lack of selectivity of the subsequent metathesis with a germanium halide GeX₄ (X = Cl, Br). This

metathesis never yields exclusively the dialkyl product. In addition, a selective direct synthesis represents the more elegant approach due to its ability to form all four new Ge–E bonds (E = C, halogen) in the target molecule in *one* synthetic step.

The variation of chain length presented here constitutes a considerable advance compared to the current synthetic route to functionalized organogermanes,^[12] because satisfactory yields were only obtained when vinyl or allyl compounds were used in the hydrogermylation step. Thus, all organo-functionalized halogermanes that are commercially available contain a C₃ chain between the tetrel and the functional groups.

The reactions described in this work require the use of the orange-colored, amorphous germanium that is obtained in the reduction of GeCl₂·dioxane (or of GeI₂) with Li[Et₃BH]. Previously reported black activated germanium, which can be obtained from GeI₂ and elemental potassium,^[13] did not react with the alkyl bromides used in this work under the given reaction conditions (Table 1), although it reacts with α -haloesters and other Reformatsky substrates at room temperature.^[13] Brown amorphous germanium, which was obtained from GeCl₄ and lithium naphthalide, did not show a reactivity analogous to the one of the orange material either. With the direct synthesis from appropriately activated germanium, a synthetic method becomes available that allows an easy, mild, and selective preparation of organofunctionalized dialkylgermanes in a single step. Furthermore, this approach shows that the kinetic inertness of the elemental tetrrels can be overcome under appropriate reaction conditions and that the exothermal nature of the direct synthesis can be exploited in a very controlled manner.

Experimental Section

The syntheses required exclusion of air and humidity and were carried out under an argon atmosphere. Typical protocol for a direct synthesis with activated germanium: GeCl₂·dioxane (232 mg, 1.0 mmol) was dissolved in THF (50 mL) and was reduced to the element with Li[Et₃BH] (2.0 mL of a 1M solution in THF). After the evolution of hydrogen had ceased, the solution was decanted from the precipitated element and the precipitate was washed with THF (3 × 50 mL). Then, five equivalents of the alkyl bromide were added and the reaction mixture was heated to 130 °C for 2 h. The orange suspension gradually turned into a colorless solution. The excess alkyl bromide was removed under vacuum.

(H₃COCC₂H₄)₂GeBr₂: ¹H NMR (CD₃CN): δ = 2.08 (t, ³J(¹H,¹H) = 7.2 Hz, 4H), 2.64 (t, ³J(¹H,¹H) = 7.2 Hz, 4H), 3.58 (s, 6H); ¹³C NMR (CD₃CN): δ = 26.2, 30.3, 52.9, 175.5; MS (EI): *m/z* (%): 377 (9) [*M* – (MeO)⁺], 327 (85) [*M* – Br⁺], 321 (100) [MeOCC₂H₄GeBr₂⁺]; yield: 82 %, colorless oil.

(H₃COCC₄H₈)₂GeBr₂: ¹H NMR (CD₃CN): δ = 1.65 (m, 8H), 1.83 (t, ³J(¹H,¹H) = 6.9 Hz, 4H), 2.34 (t, ³J(¹H,¹H) = 6.9 Hz, 4H), 3.61 (s, 6H); ¹³C NMR (CD₃CN): δ = 24.5, 27.4, 28.2, 33.9, 52.0, 174.5; MS (EI): *m/z* (%): 431 (7) [*M* – (MeO)⁺], 383 (16) [*M* – Br⁺], 349 (56) [MeOCC₄H₈GeBr₂⁺], 115 (100) [MeOCC₄H₈⁺]; yield: 84 %, colorless oil.

(NCC₂H₄)₂GeBr₂: ¹H NMR (CD₃CN): δ = 2.20 (t, ³J(¹H,¹H) = 8.1 Hz, 4H), 2.73 (t, ³J(¹H,¹H) = 8.1 Hz, 4H); ¹³C NMR (CD₃CN): δ = 13.7, 23.2, 120.4; MS (EI): *m/z* (%): 342 (3) [*M*⁺], 288 (100) [CC₂H₄GeBr₂⁺], 153 (49) [GeBr⁺]; yield: 94 %, colorless solid.

(NCC₃H₆)₂GeBr₂: ¹H NMR (CD₃CN): δ = 1.86 (m, 8H), 2.45 (m, 4H); ¹³C NMR (CD₃CN): δ = 19.1, 21.4, 26.6, 120.2; MS (EI): *m/z* (%): 369 (1)

[*M*⁺], 342 (3) [*M* – (CN)⁺], 302 (100) [CC₃H₆GeBr₂⁺], 289 (52) [(NCC₃H₆)₂GeBr⁺]; yield: 85 %, colorless solid.

(ClC₄H₈)₂GeBr₂: ¹H NMR (CD₃CN): δ = 1.92–2.04 (m, 8H), 2.05–2.11 (m, 4H), 3.64 (t, ³J(¹H,¹H) = 6.7 Hz, 4H); ¹³C NMR (CD₃CN): δ = 26.4, 36.9, 40.8, 45.2; MS (EI): *m/z* (%): 381 (3) [*M*⁺ – Cl], 325 (25) [ClC₄H₈GeBr₂⁺], 289 (23) [C₄H₈GeBr₂⁺], 243 (10) [ClC₄H₈GeBr⁺], 55 (100) [C₄H₇⁺]; yield: 84 %, colorless oil.

Received: July 20, 2001

Revised: November 15, 2001 [Z17547]

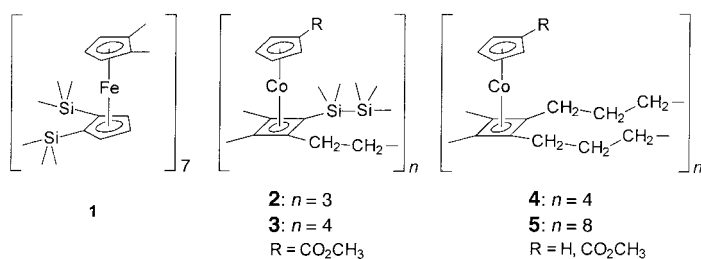
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Beltlike Macrocycles with Four and Eight (Cyclopentadienyl)(cyclobutadienyl)cobalt Building Blocks, Formed by Stepwise Oligomerization of 1,6-Cyclodecadiyne Units**

Rolf J. Schaller, Rolf Gleiter,* Jasmin Hofmann, and Frank Rominger

Dedicated to Professor Walter Siebert on the occasion of his 65th birthday

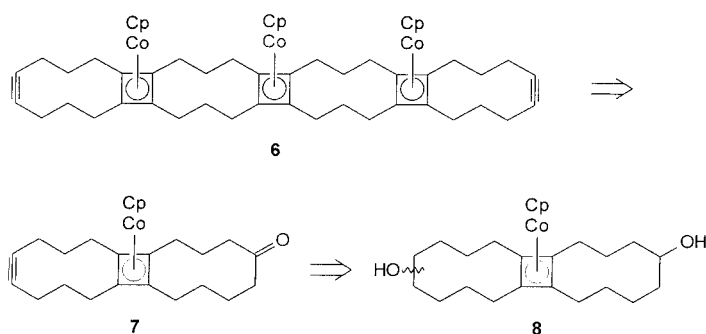
The synthesis and properties of macrocyclic compounds are important topics in supramolecular chemistry.^[1] Beltlike macrocycles with various properties can be constructed by combining different bridges and rings.^[2] These systems range from pure hydrocarbons, such as deltaphane,^[3a] and collar-ene^[3b], to polyazacycles,^[3c] cyclodextrins,^[3d] and calixar-enes^[3e], to name but a few. The acceptor properties of the interior of the belt depend upon the properties of these rings and bridges. Beltlike cyclophanes composed of redox-active π systems warrant special interest. To date, two such systems have been described, with ferrocene (**1**)^[4] and (η^5 -cyclopentadienyl)(cyclobutadienyl)cobalt [CpCo(cbd)]^[5] (**2** and **3**) as building blocks.



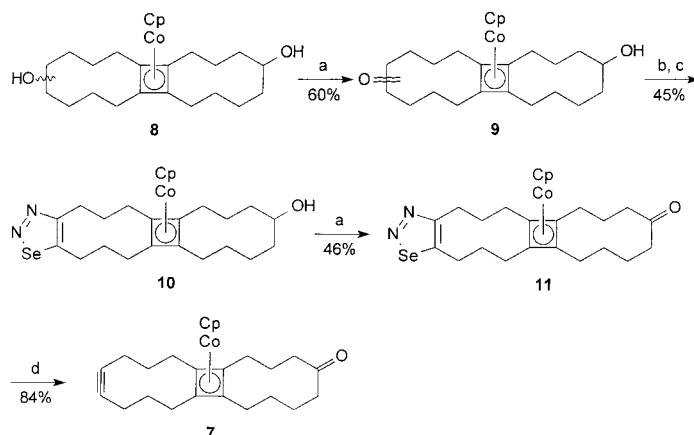
Both systems were generated by one-pot reactions. This procedure places severe limitations on the variety of ring-size and ligands. Herein, we report on a stepwise approach to beltlike macrocycles with [CpCo(cbd)] as the π system and trimethylene units as bridges.

The heptacyclic, threefold [CpCo]-capped cyclobutadiene derivative **6**, which can be prepared by cobalt-mediated dimerization of **7**, is a key compound in the stepwise construction of **4** and **5** (Scheme 1).

The tricyclic system **7** can be synthesized from the diol **8**, the preparation of which has been reported from 5-cyclodecinol.^[6] Scheme 2 shows a synthetic pathway from **8** to **7**. One of the alcohol groups of **8** was selectively oxidized with acetone/aluminum tripropan-2-olate (Oppenauer procedure^[7]) to afford **9**, which was converted to selenadiazole **10** in two



Scheme 1. Retrosynthesis of the threefold [CpCo] capped cyclobutadiene derivative **6**.



Scheme 2. Synthetic route to **7**. a) Al(*i*OPr)₃, (CH₃)₂CO, 110 °C, toluene, 1 day; b) semicarbazide acetate, EtOH, 90 °C, 2 h; c) SeO₂, HOAc, 40 °C, 5 h; d) Cu, 190 °C, 15 min.

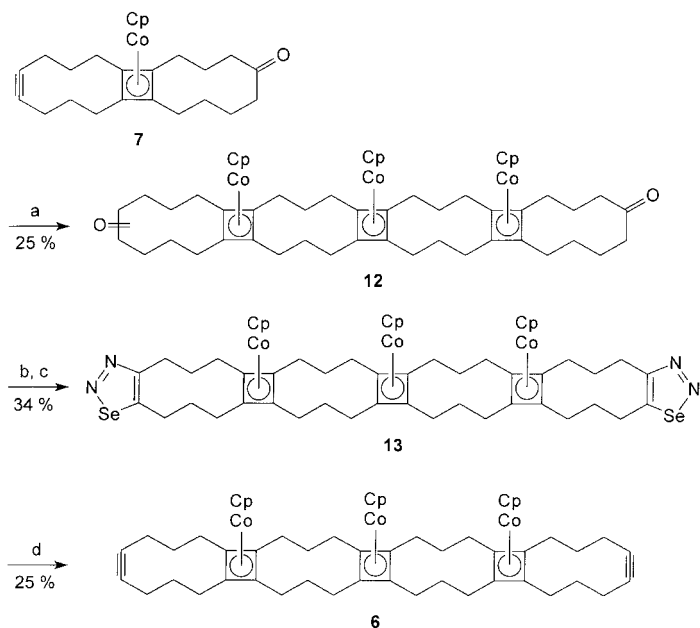
steps.^[8] First, the semicarbazone was prepared from **9** by using semicarbazide acetate. Subsequent reaction of the semicarbazone with selenium dioxide in glacial acetic acid yielded the selenadiazole **10**.^[7] Only the regioisomer shown was found. The conformation of one of the ten-membered rings in **10** is very similar to the lowest energy conformation of 1,6-cyclodecadiene. Thus it seems reasonable to assume that the regioisomer **10** is the major product.^[6] Oppenauer oxidation of **10** gave ketone **11**,^[7] the thermolysis of which in presence of finely divided copper powder yielded **7**,^[9] a key product in the synthesis of **4** ($n = 4$). The cobalt-mediated dimerization of **7** yielded three ketones (**12**), which were regioisomeric with respect to their [CpCo] fragments.^[7] The *syn* isomer was transformed into bis-selenadiazole **13**, analogously to **9** by reaction with semicarbazide acetate followed by SeO₂.^[7] Flash thermolysis of **13** in the presence of finely divided copper yielded **6**^[9] (Scheme 3).

It is noteworthy that 25% of the dimerization product of **7** was the *syn* isomer **12** (with respect to the positions of the [CpCo] fragments of the isomers). This is one third of the total yield. For steric reasons, we expected a lower yield than this. We ascribe the unexpected yield to the conformation of **7**. X-ray structural analysis of **7** (Figure 1, top) reveals that both the alkyne chain and the chain containing the oxo group adopt positions in the same half-space. Consequently, the triple bond is shielded from "back-side" attack. These steric constraints slightly favor *syn* attack on the [CpCo] moiety.

[*] Prof. Dr. R. Gleiter, Dr. R. J. Schaller, J. Hofmann, Dr. F. Rominger
Organisch-Chemisches Institut der Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-544205
E-mail: rolf.gleiter@urz.uni-heidelberg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemische Industrie, and BASF Aktiengesellschaft, Ludwigshafen.

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



Scheme 3. Synthetic route to **6**. a) [CpCo(cod)], decalin, 170 °C, 1 day; b) semicarbazide acetate, EtOH, 90 °C, 4 h; c) SeO₂, HOAc, 40 °C, 6 h; d) Cu, 190 °C, 30 min.

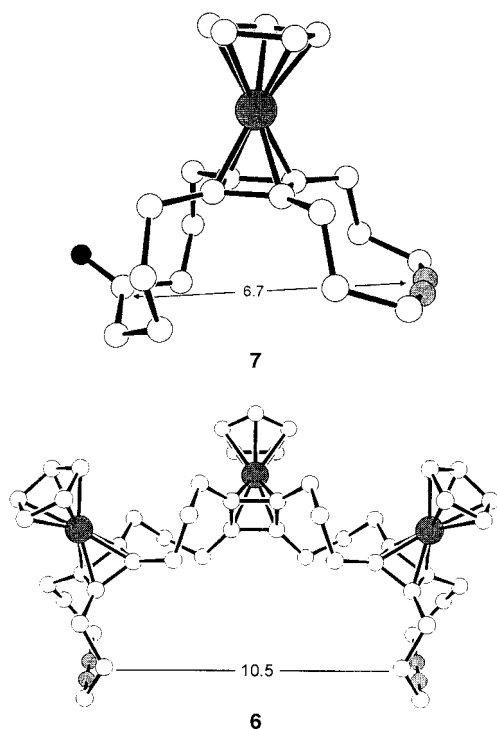


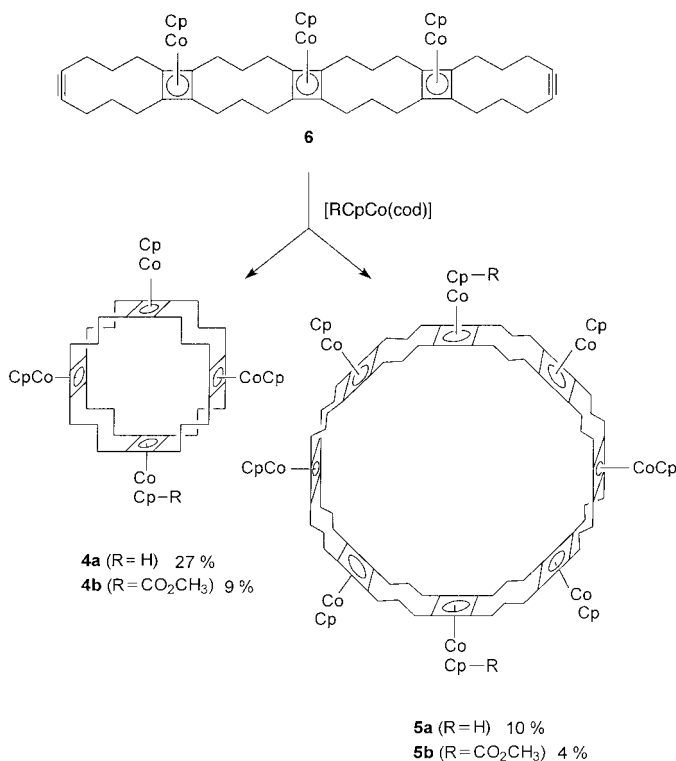
Figure 1. Structures of **6** and **7** (ORTEP plot; thermal ellipsoids for 50% probability). The hydrogen atoms are omitted for clarity. The Co atoms and the sp carbon atoms are represented as gray circles, the oxygen atom as a black circle (distances in Å).

The observed *syn-anti* ratio of 1:2 suggests that several conformations of **7** exist in solution.

The conformation of **6** in the solid state is also interesting (Figure 1, bottom). The *syn* position of all three {CpCo} fragments forces the two alkyne chains towards each other, which leads to a distance of about 10.5 Å, in a tweezerlike arrangement.^[2, 10] The flexibility of the ten-membered-ring

units should provide enough mobility to allow the possibility of a cobalt-induced ring closure and formation of inclusion complexes.

The reaction of **6** with [RCpCo(cod)] (R = H or CO₂CH₃; cod = cyclooctadiene) at high dilution afforded two compounds in each case (Scheme 4). The masses calculated for the main products of the intramolecular ring closure were in



Scheme 4. Reaction of **6** with [RCpCo(cod)].

accord with those for the tetramers **4a** and **4b**, determined by high-resolution mass spectrometry.^[11] The high level of symmetry in **4a** results in only four signals in the ¹³C NMR spectrum. The signal for the sp hybridized carbon atoms in the cyclobutadiene unit is observed at $\delta = 84.0$; those for the Cp carbon atoms are shifted up field, to $\delta = 80.3$. Signals arising from both methylene-carbon atoms appear at $\delta = 32.4$ and $\delta = 28.4$, in a ratio of 1:2. In the ¹H NMR spectrum, a singlet is observed at $\delta = 4.57$, which is attributed to the cyclopentadienyl protons, and the signals from the two methylene groups occur at $\delta = 2.37$ and $\delta = 2.04$. The side products of the intermolecular [2+2] cycloaddition had masses of exactly twice those of **4a** and **4b**, respectively. Based on the analytical data, we assign the octameric structures **5a** and **5b** to these products, respectively.^[10] Quasi-linear oligomers were not detected.

The stepwise approach described permits the synthesis of macrocyclic systems of the types **4** and **5**. This widens the potential for the synthesis of even-numbered beltlike cyclophanes containing organometallic π systems. It should now be possible to study the acceptor properties of the interior of such a cavity.

Received: December 3, 2001 [Z18323]

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- [9] Relevant analytical data for **6** and **7**. Compound **6**: yellow needles, m.p.: 139 °C; IR (KBr): $\tilde{\nu}$ = 2920 (CH₂), 1630 cm⁻¹ (C=C); UV (CH₂Cl₂): λ_{max} (log ϵ) = 364 (2.35), 302 (3.24), 268 nm (4.31); ¹H NMR (500 MHz, C₆D₆): δ = 4.88 (s, 5H; CH), 4.70 (s, 10H; CH), 2.17–1.75 (m, 48H; CH₂); ¹³C NMR (125 MHz, C₆D₆): δ = 82.9 (C_{cbd}), 81.9 (C₌), 80.2 (C_{cp}), 79.8 (C_{cbd}), 79.5 (C_{cp}), 79.0 (C_{cbd}), 32.0 (CH₂), 27.7 (CH₂), 25.5 (CH₂), 25.1 (CH₂), 24.1 (CH₂), 19.4 (CH₂); HRMS (FAB) calcd for C₅₅H₆₃Co₃: 900.2926, found: 900.2861; elemental analysis [%] calcd for C₅₅H₆₃Co₃ · 2CH₂Cl₂: C 63.94, H 6.31, found: C 63.71, H 6.23; X-ray structure analysis of C₅₆H₆₅Cl₂Co₃: M_r = 985.77, μ = 1.184 mm⁻¹, ρ_{calcd} = 1.378 g cm⁻³, orthorhombic, space group *Pnma*, Z = 4, a = 18.1815(3), b = 30.8148(5), c = 8.4824(1) Å, V = 4752.34(12) Å³, crystal dimensions 0.36 × 0.30 × 0.02 mm³, T = 200(2) K, λ = 0.71073 Å, θ -range 2.24–27.48°, $-23 \leq h \leq 23$, $-40 \leq k \leq 39$, $-11 \leq l \leq 10$; 46 290 reflections collected, 5531 unique reflections, 2889 observed reflections with $I > 2\sigma(I)$, transmission max/min 0.98/0.86, an empirical absorption correction was applied by using SADABS,^[12] based on the Laue symmetry of the reciprocal space. The structure was refined against F^2 with a full-matrix least-squares algorithm, $R(F)$ = 0.054, $\omega R_2(F^2)$ = 0.092. Hydrogen atoms were included in calculated positions. Special position of the molecule on a crystallographic mirror plane, one equivalent of dichloromethane is cocrystallized. Compound **7**: orange crystals; m.p.: 144 °C; IR (KBr): $\tilde{\nu}$ = 2931 (CH₂), 1699 cm⁻¹ (C=O); UV (CH₂Cl₂): λ_{max} (log ϵ) = 380 (2.75), 300 (2.20), 268 nm (4.42); ¹H NMR (300 MHz, C₆D₆): δ = 4.45 (s, 5H; CH), 2.83–1.15 (m, 26H; CH₂); ¹³C NMR (75 MHz, C₆D₆): δ = 211.7 (C=O), 82.8 (C_{cbd}), 82.3 (C_{cbd}), 81.5 (C_{cp}), 80.9 (C_{cbd}), 79.0 (C₌), 45.2 (CH₂), 36.2 (CH₂), 29.3 (CH₂), 27.6 (CH₂), 26.4 (CH₂), 24.4 (CH₂), 23.9 (CH₂), 22.9 (CH₂), 20.8 (CH₂), 20.2 (CH₂); HRMS (FAB) calcd for C₂₅H₃₁CoO: 406.1706, found: 406.1711; elemental analysis [%] calcd for C₂₅H₃₁CoO: C 73.87, H 7.69; found: C 73.76, H 7.66. X-ray structure analysis of C₂₅H₃₁CoO: M_r = 406.43, μ = 0.848 mm⁻¹, ρ_{calcd} = 1.316 g cm⁻³, orthorhombic, space group *Pbca*, Z = 8, a = 14.4938(1), b = 10.3639(1), c = 27.4912(1) Å, V = 4103.87(5) Å³, crystal dimensions 0.26 × 0.18 × 0.06 mm³, T = 200(2) K, λ = 0.71073 Å, θ -range 1.48–25.60°, $-17 \leq h \leq 17$, $-12 \leq k \leq 12$, $-32 \leq l \leq 32$; 28 757 reflections collected, 3684 unique reflections, 2418 observed reflections with $I > 2\sigma(I)$, transmission max/min 0.95/0.80, an empirical absorption correction was applied by using SADABS,^[12] based on the Laue symmetry of the reciprocal space. The structure was refined against F^2 with a full-matrix least-squares algorithm, $R(F)$ = 0.041, $\omega R_2(F^2)$ = 0.094. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were refined isotropically. CCDC-173922 (**7**) and CCDC-173921 (**6**) 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 (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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- [11] Relevant analytical data of **4** and **5**. **4a**: HRMS (FAB) calcd for C₆₀H₆₈Co₄: 1024.2649; found: 1024.2693; ¹H NMR (500 MHz, C₆D₆): δ = 4.57 (s, 20H; CH), 2.37 (m, 16H; CH₂), 2.04 (m, 32H; CH₂); ¹³C NMR (75 MHz, C₆D₆): δ = 84.0 (C_{cbd}), 80.3 (C_{cp}), 32.4 (CH₂), 28.3 (CH₂). **4b**: HRMS (FAB) calcd for C₆₂H₇₀Co₄O₂: 1082.2704, found: 1082.2699. **5a**: HRMS (FAB) calcd for C₁₂₀H₁₃₇Co₈: 2049.5376, found: 2049.5371. **5b**: HRMS (FAB) calcd for C₁₂₄H₁₄₀Co₈O₄: 2164.5408, found: 2164.5391.
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A *trans*-Platinum(II) Complex as a Single-Molecule Insulator**

Marcel Mayor,* Carsten von Hänisch, Heiko B. Weber,* Joachim Reichert, and Detlef Beckmann

The use of single molecules as the ultimate tiny building blocks for electronic circuits would be an enormous step in terms of size reduction. This visionary concept in molecular electronics has its roots in theoretical studies of the 1970s.^[1] A profound understanding of the correlation between the molecular structure and physical properties of single molecules is absolutely necessary for the design of such electronic circuits.^[2] Numerous predictive correlation studies have been elaborated on the basis of electrochemical and/or spectroscopic investigations in solutions of different types of molecular wires^[3] and monodisperse oligomers,^[4] such as *trans*-platinum-linked oligo(tetraethylenethenes).^[5]

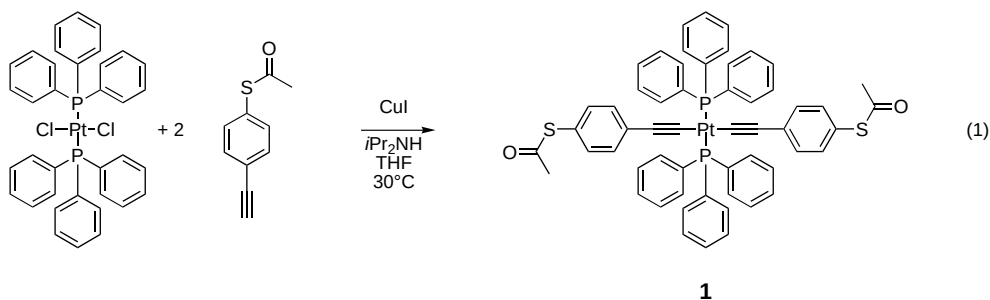
Studies on electron transport through single-layer molecular films have been carried out between metallic electrodes.^[6] Scanning tunneling microscopy has been used to investigate single or small numbers of molecules,^[7] for example, in the switching behavior of molecular films supporting gold nano-clusters.^[8] However, there are only a few studies on electron transport through single molecules which are covalently linked between two electrodes. Mechanically controlled break junctions have proven to be a very powerful tool for such investigations.^[9] In previous work we studied the current through conjugated organic molecules^[10] and generated

[*] Dr. M. Mayor, Dr. H. B. Weber, Dr. C. von Hänisch, J. Reichert, Dr. D. Beckmann
Forschungszentrum Karlsruhe GmbH
Institut für Nanotechnologie
Postfach 3640, 76021 Karlsruhe (Germany)
Fax: (+49) 7247-82-6369
E-mail: marcel.mayor@int.fzk.de

[**] This work was supported by the Strategiefond from the Helmholtz Foundation.

strong arguments that single molecules can indeed be studied in such a break junction. The enlargement of the “molecular toolbox” for the design of stiff, rodlike molecules with tailor-made conductivities has led us to consider *trans*-acetylene–platinum(II) complexes. The platinum–acetylene bond has hardly any π character and thus separates the molecular rod into two independent conjugated systems. This arrangement should therefore increase its resistance.^[5]

Here we present the synthesis and characterization of the platinum(II) complex **1** [Eq. (1)]. The complex has a molecular rod structure consisting of two conjugated π systems coordinated in a *trans* arrangement to a platinum(II)



ion. Acetyl-protected sulfur functions at both ends of the rod allow for its immobilization between two gold electrodes. Deprotection of **1** in the presence of the gold surfaces of a mechanically controlled break junction gave **1'** anchored to the two gold electrodes through the two sulfur atoms (Figure 1).

Compound **1** was synthesized as shown in Equation 1 by a similar protocol as that described in ref. [5]; a solution of *trans*-bis(triphenylphosphane)platinum(II) chloride in THF, diisopropylamine (as base), and copper iodide (as catalyst) was treated with (4-ethynyl)phenyl thioacetate at 30 °C. The resulting ivory-colored solid was characterized by matrix-

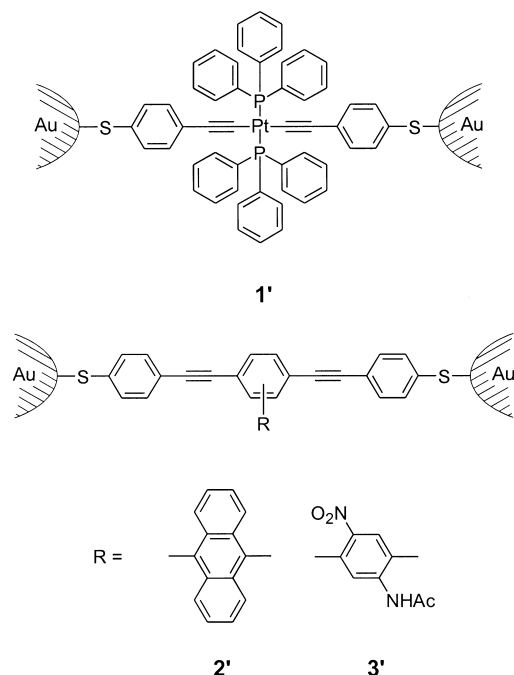


Figure 1. Organic–inorganic hybrid structure of **1'** and organic compounds **2'** and **3'** immobilized between two gold electrodes.

assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and ^1H , ^{13}C , and ^{31}P NMR spectroscopy as well as by X-ray analysis. Slow evaporation of a chloroform solution provided single crystals that were suitable for X-ray structure determination. The two triplets ($\text{C}\equiv\text{C}-\text{Pt}_\alpha$: $^2J_{\text{PC}} = 6.2$ Hz, $\text{C}\equiv\text{C}-\text{Pt}_\beta$: $^3J_{\text{PC}} = 5.4$ Hz) observed in the ^{13}C NMR spectrum of **1** suggested a *trans* conformation of the acetylene groups, which was confirmed by the crystal structure determination (Figure 2). Compound **1** crystallizes in the triclinic space group $P\bar{1}$, with one molecule in the unit cell.^[11] The platinum ion is coordinated in a square-planar arrangement by two *trans*-PPh₃ groups and two *trans*-acetylene ligands. The intramolecular sulfur...sulfur distance determined from the crystal structure is 1.843(33) nm.

The mechanically controlled break-junction technique enabled the two gold electrodes to be adjusted with sub-angstrom resolution.^[9b, 12] At the beginning of the experiment the electrodes were fixed at a distance of 10 nm and exposed to a 5×10^{-4} M solution of **1** in THF for 30 s. The thioacetyl protecting group is readily hydrolyzed on the gold surface and a covalent sulfur–gold bond is formed.^[10, 13] The gold surface of the electrodes is now partially covered by molecules which are covalently linked to the surface on one

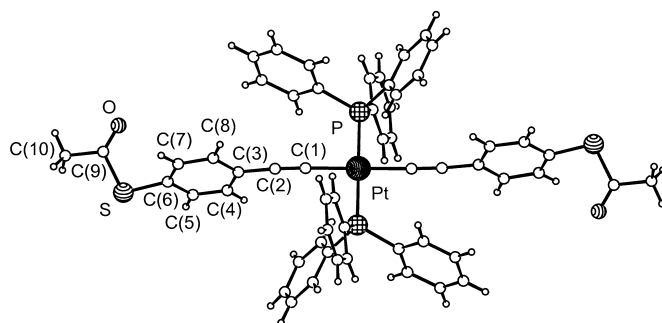


Figure 2. Molecular structure of **1** in the crystal. Selected bond lengths [pm] and bond angles [°]: Pt–P 231.77(15), Pt–C(1) 202.7(6), C(1)–C(2) 117.9(9), C(2)–C(3) 145.0(8), C(6)–S 177.8(6), S–C(9) 178.7(6), C(9)–O 118.1(9), C(9)–C(10) 149.6(10); P–Pt–C(1) 90.94(17), P'–Pt–C(1) 89.06(17), Pt–C1–C2 174.4(6), C1–C2–C3 173.7(8), C(6)–S–C(9) 103.0(3), S–C(9)–C(10) 111.0(6), S–C(9)–O 123.4(5), O–C(9)–C(10) 125.6(7).

side, while the second sulfur atom is still protected by an acetyl group. The acetyl protecting group also prevents oxidative disulfide formation, and is only cleaved by contact with the second gold electrode.^[13] After a short exposure of the break junction to the solution of **1** it was extensively rinsed with THF and subsequently transferred to a vacuum (5×10^{-7} mbar). The two gold electrodes were then slowly moved toward each other while the current was monitored at a bias voltage of 4 V. A sudden “lock-in” behavior with an immediate increase of the current to a plateau of about 0.2 nA was indicative of the first bridging contact of a molecule between the two electrodes. This observed current plateau is insensitive to small variations in the distance

between the electrodes. However, an increase in the current was observed on further pushing the two electrodes together. This phenomenon can be explained by additional contributions of further molecules that bridge the electrodes at smaller distances. In some cases a doubling of the current was observed, which is the expected behavior for the bridging of a second molecule, followed by a further drastic increase in the current as the electrodes further approach one another. However, currents smaller than 0.2 nA (the first plateau) were never observed.

The configuration is stable at room temperature and reproducible I/V curves could be recorded. Experiments have shown that such a stable, reproducible behavior could not be obtained without molecules between the electrodes; gold-vacuum-gold setups were unstable, presumably because of the high mobility of gold atoms at the surface. The overall behavior of our experiment resembles the observations already made for the organic systems **2'** and **3'**. A comparison of the I/V curves with the spatial symmetry of the molecules (together with further considerations) in these systems showed that single molecules could indeed be observed.^[10] Therefore, we are convinced that in our described experiment we observe electron transport through a single molecule covalently linked on both sides to gold electrodes.

The I/V curves recorded on **1'** immobilized in the gold break junction are shown in Figure 3. The curves are symmetric with respect to voltage inversion, as expected for the symmetric structure of **1'**. An exponential increase in the

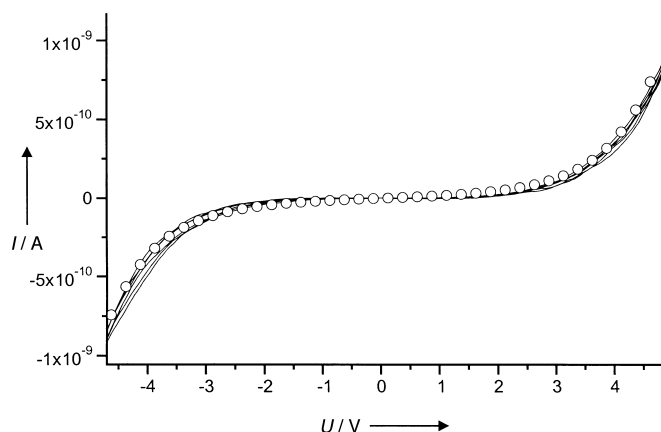


Figure 3. I/V curves for a gold-**1'**-gold setup. Consecutively recorded I/V curves (solid lines) and simulated current with a barrier height of 2.5 eV (circles) are shown.

current with applied voltage is observed, which corresponds to the behavior of a classical insulator. The resistance of the organic–inorganic hybrid structure **1'** between the two gold electrodes at 5 V is in the range of 5–50 G Ω , which is about three orders of magnitude larger than that observed for the organic compounds **2'** and **3'**. The current/voltage relationship can best be described by the model for a rectangular tunnel barrier,^[14] with a tunnel barrier height of 2.5 eV giving the best fit to our data (circles in Figure 3). The origin of the insulating behavior of **1'** can be explained by the pure σ character of the Pt–C(sp) bonds between the Pt^{II} ion and the acetylene ligands.^[15] However, both the stability of the setup and the

stability of the insulating behavior up to such a high bias voltage of 5 V are remarkable.

The results indicate the potential of platinum(II) complexes as single-molecule electronic junctions. Measurement of the current transport through single molecules provide important insight for controlling and tuning electron transport through molecular structures, a crucial requirement for the design of electronic circuits based on single to small numbers of molecules.

Experimental Section

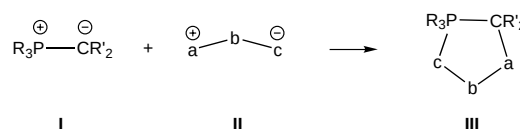
(4-ethynyl)phenyl thioacetate (30.5 mg, 173 mmol) was dissolved in N₂-saturated THF (10 mL). *trans*-Bis(triphenylphosphane)platinum(II) chloride (60.7 mg, 76.8 mmol) and copper iodide (3.6 mg, 18.9 mmol) were added, followed by diisopropylamine (1 mL). The reaction mixture was stirred at 30 °C under a N₂ atmosphere for 1 h. Filtration through silica with THF and subsequent column chromatography (silica gel, CH₂Cl₂/toluene 1/1–3/1) yielded **1** (12.6 mg, 11.8 mmol, 15%) as an ivory solid. M.p. 205 °C (decomp); ¹H NMR (300 MHz, CDCl₃): δ = 7.72–7.85 (m, 12H), 7.31–7.42 (m, 18H), 6.94 (d, J = 8 Hz, 4H), 6.27 (d, J = 8 Hz, 4H), 2.33 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 194.75, 135.03 (t, C $\equiv$ C–Pt₂, ² J_{PC} = 6.2 Hz), 133.18, 131.56, 131.20, 130.81, 130.32, 129.05, 128.24, 127.91 (t, C $\equiv$ C–Pt₂, ³ J_{PC} = 5.4 Hz), 123.22, 30.04; ³¹P{¹H} NMR (121.5 MHz, CDCl₃): δ = 20.02 (s, J_{PtP} = 2630 Hz); MALDI-TOF-MS: 1071.55 [M^+ + H], 894.46 [M^+ – C $\equiv$ CPhSAc], 719.38 [M^+ – 2 C $\equiv$ CPhSAc].

Nanostructured mechanically controlled break junctions were fabricated as described in ref. [12]. This setup allows the distance of the gap to be adjusted with sub-angstrom resolution. A 5×10^{-4} M solution of **1** in THF was applied for 30 s, and the junction was subsequently rinsed with THF under a N₂ atmosphere. The controlled approach of the two electrodes and transport measurements were investigated in a metallic ultrahigh-vacuum box at 5×10^{-7} mbar with a Keithley 6430 subfemtoamp remote source meter.

Received: September 27, 2001 [Z17979]

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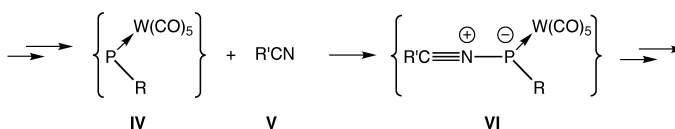
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- [11] **1**: $a = 964.8(2)$, $b = 1079.9(2)$, $c = 1271.7(3)$ pm, $\alpha = 76.69(3)$, $\beta = 75.67(3)$, $\gamma = 64.67(3)^\circ$, $V = 1148.6(4) \times 10^6$ pm³; triclinic, space group $P\bar{1}$, $Z = 1$, $\rho_{\text{calc}} = 1.547$ g cm⁻³, $\mu = 3.258$ mm⁻¹, STOE IPDS2, MoK α radiation, $\lambda = 0.71073$ Å, $T = 200$ K, $2\theta_{\text{max}} = 52^\circ$; 5297 reflections measured, 3692 independent reflections ($R_{\text{int}} = 0.0312$), 3690 independent reflections with $F_o > 4\sigma(F_o)$. The structure was solved by direct methods and refined by full-matrix least-square techniques against F^2 , 286 parameters (Pt, P, S, O, C refined anisotropically, H atoms were calculated at ideal positions); $R1 = 0.0401$; $wR2 = 0.1058$ (all data); GOF = 1.058; max. residual electron density 1.032 e Å⁻³. CCDC 169386 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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Scheme 1. Cycloaddition of Wittig ylides with 1,3-dipoles (R, R' = arbitrary organic substituents; a, b, c denote organoelement fragments).

as a 2π -cycloaddition component, were unknown (as indeed were similar reactions involving any other benzene derivatives^[3]). Cyclometalations of *P*-phenyl Wittig ylide derivatives are known, but are rare; they have been observed, for example, in reactions with zirconium^[4] and platinum^[5] complexes.

Nitrilium phosphane ylide complexes **VI**, whose existence as intermediates we were able to demonstrate by trapping reactions,^[6] now represent a new and well-established 1,3-dipole system in heterocyclic chemistry.^[7–9] We recently discovered the 1,1-addition of electrophilic terminal phosphanediyl complexes **IV** to nitriles **V**, providing an independent access to **VI** (Scheme 2), so that the synthetic potential of **VI** could be extended further by the use of 7-phosphanorbornadiene complexes.^[10, 11]



Scheme 2. Formation of nitrilium phosphane ylide complexes by 1,1-addition of electrophilic terminal phosphanediyl complexes with nitriles (R, R' = arbitrary organic substituents).

Intramolecular [3+2] Cycloaddition of a Nitrilium Phosphane Ylide Complex to the *P*-Phenyl Group of a Wittig Ylide**

Nils Hoffmann, Peter G. Jones, and Rainer Streubel*

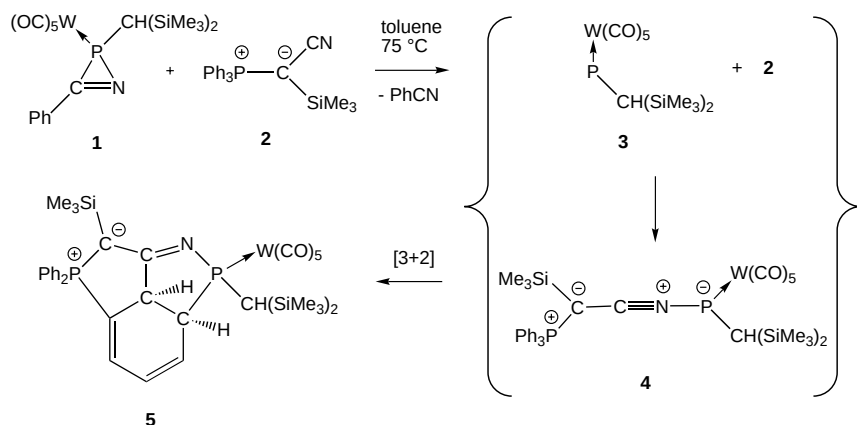
Dedicated to Professor Masaaki Yoshifuji
on the occasion of his 60th birthday

Wittig ylides^[1, 2] of the general type $R_3PCR'_2$ **I** are some of the most widely used and thus most extensively investigated phosphorus compounds in organic synthesis; cycloaddition reactions such as those of **I** with 1,3-dipoles **II** belong to the classical repertoire of heterocyclic chemistry. Such reactions, which exploit the P,C-ylide function, generally proceed smoothly and lead to the five-membered phosphorus(v) heterocycles **III** (Scheme 1).^[1] Until now, cycloadditions to a *P*-bonded phenyl group of Wittig ylides, involving the former

For some time we have been investigating the possibility of obtaining kinetically stabilized nitrilium phosphane ylide complexes, in order to study their properties. Promising candidates in this respect are, for example, Wittig ylide derivatives that contain a nitrile function at the ylide carbon atom. Because of their variable stereoelectronic properties, these are potential reaction partners for 1,1-additions to **IV**. Surprisingly, however, heating the 2*H*-azaphosphirene complex **1**^[12] in toluene in the presence of the Wittig ylide derivative **2**^[13] led diastereoselectively to the new tricycle **5**, whose formation we explain by a [3+2] cycloaddition of the intermediate 1,3-dipole **4** to a phenyl group of **2** (Scheme 3). Monitoring the reaction by ³¹P NMR spectroscopy indeed revealed the appearance and disappearance of a further product ($\delta = 22.3$ (d), $J(P,P) = 10.8$, $^1J(W,P) = 243.9$ Hz) and -0.7 (d)), which however could not be more precisely characterized because it was a minor component of the product mixture. A previous study using other, sterically more demanding, ylide-C-substituted triorganosilyl derivatives of **2** provided support for our interpretation via 1,1-addition as a primary step, in that here also the same tricyclic ring systems were formed as in **5**.^[14] The results presented here are also interesting in view of recently reported first examples of reactions of other benzene derivatives with μ^1 - and μ^2 -phosphanediyl complexes. In the first case a [5]metacyclopentadiene^[15] reacted as a 4π -cycloaddition component,^[16] whereas the second example involved the phenyl group of benzonitrile

[*] Prof. Dr. R. Streubel, Dipl.-Chem. N. Hoffmann, Prof. Dr. P. G. Jones
Institut für Anorganische und Analytische Chemie
Technische Universität Braunschweig
Postfach 3329, 38023 Braunschweig (Germany)
Fax: (+49) 531-391-5387
E-mail: r.streubel@tu-bs.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie; we thank Andreas Weinkauff for recording the X-ray data.


 Scheme 3. Suggested reaction sequence for the formation of complex **5**.

in a complicated reaction sequence of C–H activation and cyclization^[17]—the aromatic 6 π -electron system, however, remained intact.

The constitution of complex **5** was established from NMR and MS data^[18] and confirmed (Figure 1) by X-ray structure analysis.^[19] The presence in solution of the tricycle **5** (rather than the isomeric nitrilium phosphane ylide complex **4**) is

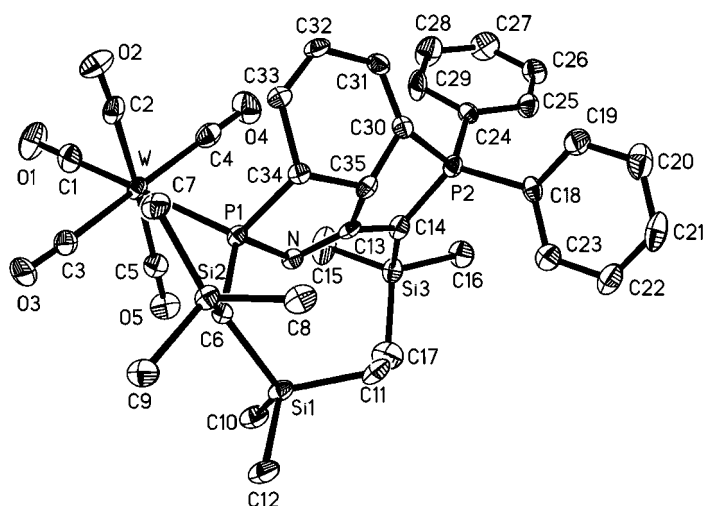
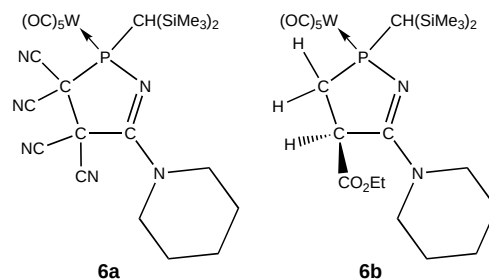


Figure 1. Molecular structure of complex **5** in the crystal (ellipsoids represent 50 % probabilities; hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: W–P1 2.5172(15), P1–C6 1.846(6), P1–N 1.693(4), P1–C34 1.903(6), C13–N 1.299(7), C13–C14 1.433(2), P2–C14 1.721(7), P2–C30 1.802(6), C30–C35 1.498(8), C35–C13 1.541(8), C35–C34 1.536(7), C34–C33 1.498(8); N–P1–C34 95.8(2), P1–C34–C35 103.0(4), C34–C35–C13 108.5(5), C35–C13–N 117.8(5), C13–N–P1 113.2(4), P2–C14–Si3 128.5(3), C13–C14–P2 107.3(4), C13–C14–Si3 123.1(5).

unambiguously shown by the observation of two resonance signals from both four-coordinate carbon atoms of the former phenyl ring at $\delta = 54.2$ and 50.5. The identification of the signals was facilitated by significant differences in the magnitudes of the coupling constants, for example 75.7 and 13.2 Hz for the carbon atom bonded to the 1,2-azaphosphole phosphorus. The $^{13}\text{C}\{^1\text{H}\}$ NMR data of the 1,2-azaphosphole moiety of complex **5** are generally similar to values of related compounds, for example, the 3,3',4,4'-tetracyano-1,2-azaphospholene-tungsten complex **6a**^[20] (Figure 2); the marked

deshielding of the imino carbon atom in complex **5** ($\delta = 183.6$, cf. $\delta = 144.9$ in **6a**) is thus unexpected. A comparison of the ^{31}P NMR data of **5** and **6a** is also interesting; the resonance signal of the 1,2-azaphosphole phosphorus atom in **5** ($\delta = 159.8$) is very close to that of **6a** ($\delta = 158.5$), which is surprising in view of the differing substitution patterns at the sp^3 carbon atoms of the 1,2-azaphosphole moieties.

The molecular structure of complex **5** confirms the assumption of a cisoid linkage of the terminal atoms of the 1,3-dipole with the C_2 element of the phenyl group, and shows a marked cyclohexa-1,3-diene structure for the ring (C33–C32 1.319(8), C32–C31 1.452(8), C31–C30 1.333(8) Å). Otherwise, most dimensions of the 1,2-azaphosphole moiety are as expected and correspond closely to those of the 1,2-azaphospholene-tungsten complex^[21] **6b** (Figure 2), except for the P1–C34 distance in **5** of 1.903(6) Å (1.851(5) Å in **6b**). The former value indicates a significantly lengthened single bond (the standard value of a C_{sp^3} – P^{III} single bond is 1.855 Å).^[22] The tricyclic ring system in **5** displays the approximate shape of a flattened dish, in which the atom C35 marks the lowest point of the ring framework, lying 0.5 Å from the plane C13–C30–C34. The pentacarbonyltungsten group is *endo* at P1.


 Figure 2. Complexes **6a** and **6b**.

Experimental Section

5: A solution of complex **1** (0.62 g, 1 mmol) and the Wittig ylide **2** (0.38 g, 1 mmol) in toluene (6 mL) was heated with constant stirring to 75 °C for about 2 h; the end of the reaction was determined by ^{31}P NMR spectroscopy. The solution was evaporated to dryness in vacuo (ca. 0.1 mbar) and the residue was separated by column chromatography (SiO_2 , –15 °C, petroleum ether/diethyl ether 2:1). Removal of the solvent and recrystallization from diethyl ether at –20 °C gave **5** as yellow crystals. Yield: 0.48 g (51 %), m.p. 61 °C (decomp); ^1H NMR (200.0 MHz, CDCl_3 , 25 °C, ext. TMS): $\delta = 0.01$ (s, 9H; SiMe_3), 0.19 (s, 9H; SiMe_3), 0.26 (s, 9H; SiMe_3), 1.73 (d, $^3J(\text{P,H}) = 10.0$ Hz, 1H; $\text{CH}(\text{SiMe}_3)_2$), 3.37 (m, 1H; CH), 3.60 (dd, $^3J(\text{P,H}) = 17.0$ Hz, $^4J(\text{P,H}) = 6.4$ Hz, 1H; CH), 6.10 (m, 2H; sp^2 -CH), 6.34 (m, 1H; sp^2 -CH), 7.35 (m, 4H; Ph), 7.60 (m, 4H; Ph), 7.86 (m, 2H; Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CDCl_3 , 25 °C, ext. TMS): $\delta = 0.9$ (d, $J(\text{P,C}) = 2.4$ Hz; SiMe_3), 2.4 (d, $J(\text{P,C}) = 2.6$ Hz; SiMe_3), 2.5 (s; SiMe_3), 30.3 (d, $^1J(\text{P,C}) = 13.3$ Hz; $\text{CH}(\text{SiMe}_3)_2$), 39.7 (m br; PCCN), 50.5 (dd, $J(\text{P,C}) = 22.1$ Hz, $J(\text{P,C}) = 15.3$ Hz; CHP), 54.2 (dd, $J(\text{P,C}) = 75.7$ Hz, $J(\text{P,C}) = 18.5$ Hz; CHP), 120.2 (dd, $J(\text{P,C}) = 12.8$ Hz, $J(\text{P,C}) = 8.5$ Hz; sp^2 -CH), 124.1 (pt, $J(\text{P,C}) = 4.3$ Hz; sp^2 -CH), 125.1 (dd, $^1J(\text{P,C}) = 86.5$ Hz, $^3J(\text{P,C}) = 4.9$ Hz; sp^2 -CP), 125.3 (d, $^1J(\text{P,C}) = 88.8$ Hz; *ipso*-Ph), 126.2 (d, $^1J(\text{P,C}) = 80.4$ Hz; *ipso*-Ph), 128.9 (d, $^3J(\text{P,C}) = 12.8$ Hz; *m*-Ph), 129.2 (d, $^3J(\text{P,C}) = 12.0$ Hz; *m*-Ph), 130.1 (pt, $J(\text{P,C}) = 3.6$ Hz; sp^2 -CH), 132.5 (d, $^2J(\text{P,C}) = 10.6$ Hz; *o*-Ph), 132.6 (d, $^4J(\text{P,C}) = 4.4$ Hz; *p*-Ph), 133.2 (d, $^4J(\text{P,C}) =$



3.1 Hz; *p*-Ph), 134.0 (d, $^3J(\text{P,C}) = 11.2$ Hz; *o*-Ph), 183.6 (dd, $^2J(\text{P,C}) = 16.4$ Hz, $^3J(\text{P,C}) = 10.7$ Hz; PCCN), 198.9 (d, $^2J(\text{P,C}) = 7.9$ Hz; *cis*-CO), 202.5 (d, $^2J(\text{P,C}) = 23.4$ Hz; *trans*-CO); $^{31}\text{P}\{^1\text{H}\}$ NMR (81.0 MHz, CDCl_3 , 25 °C, ext. 85% H_3PO_4): $\delta = 46.4$ (d, $^4J(\text{P,P}) = 5.1$ Hz; PPh_2), 159.8 (d, $^1J(\text{W,P}) = 260.9$ Hz; PW).

Received: November 9, 2001 [Z18194]

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- [18] **5**: MS (positive-ion FAB (nitrobenzyl alcohol), ^{184}W): m/z (%) 888 (20) $[\text{M}+\text{H}]^+$, the isotope pattern is in agreement with calculation.
- [19] Crystal structure of complex **5** ($\text{C}_{35}\text{H}_{43}\text{NO}_5\text{P}_2\text{Si}_3\text{W}$): triclinic, space group $P\bar{1}$, $a = 10.9277(12)$, $b = 13.3245(16)$, $c = 13.7618(16)$ Å, $\alpha = 90.325(6)^\circ$, $\beta = 91.388(6)^\circ$, $\gamma = 103.281(6)^\circ$, $V = 1934.9$ Å³, $Z = 2$, $\mu = 5.0$ mm⁻¹, $T = -140^\circ\text{C}$. A yellow tablet with dimensions of about $0.1 \times 0.1 \times 0.03$ mm was mounted in perfluoropolyether oil on a Bruker SMART 1000 CCD diffractometer. Intensity data were registered to $2\theta_{\text{max}} = 52^\circ$ ($\text{MoK}\alpha$). Of a total of 24130 reflections, 7889 were independent ($R_{\text{int}} = 0.073$). After a semiempirical absorption correction (SADABS), the structure was solved with the heavy-atom method and refined anisotropically against F^2 (program SHELXL-97, G. M. Sheldrick, University of Göttingen. Hydrogen atoms were included by using a riding model or as rigid methyl groups. Final $wR2$ (all data) = 0.0808, conventional $R1 = 0.042$, 433 parameters; $S = 0.922$; max. $\Delta\rho = 1.861/-1.953$ e Å⁻³. CCDC-173084 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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Self-Assembly of ZnO: From Nanodots to Nanorods**

Claudia Pacholski, Andreas Kornowski, and
Horst Weller*

Bottom-up techniques for the fabrication of small particles, which mostly arise from colloid chemistry, are integral components in nanotechnology and materials manufacturing. Control of particle size, shape, and crystalline structure represent some of the key issues in this area. Classical models describe the genesis of particles by the formation of tiny crystalline nuclei in a supersaturated medium followed by crystal growth. The latter process is controlled by mass transport and by the surface equilibrium of addition and removal of individual monomers, that is atoms, ions, or molecules. Hereby, the driving force for monomer removal (dissolution) increases with decreasing particle size. Thus, within an ensemble of particles with slightly different sizes the large particles will grow at the cost of the small ones. This mechanism is called Ostwald ripening and is generally believed to be the main path of crystal growth.

A different view of crystal growth is emerging from recent experiments by Penn and Banfield.^[1–3] They observed that anatase and iron oxide nanoparticles with sizes of a few nm can coalesce under hydrothermal conditions in a way they call “oriented attachment”. In the so formed aggregates, the crystalline lattice planes may be almost perfectly aligned or dislocations at the contact areas between the adjacent particles lead to defects in the finally formed bulk crystals. They presented strong evidence that this type of crystal growth plays an important role in earth history during mineral formation. Oriented attachment was also proposed by other authors during crystal growth of TiO_2 ^[4] and for micrometer-sized ZnO particles during the formation of rodlike ZnO microcrystals.^[5] The latter experiments give, however, only indirect evidence.

Self-assembly of colloidal particles into larger aggregates is not principally new. The formation of secondary particles with typical sizes in the micrometer regime is a well-known phenomenon in classic colloid chemistry.^[6] Kinetic models for this type of growth have been developed which do, however, not consider the process on an atomic level nor give attention to crystallographic orientation of the aggregated particles. Indeed, the X-ray diffraction (XRD) pattern of those secondary particles usually indicate polycrystalline morphology.

Recently, self-assembly of ligand-stabilized nanoparticles with sizes of a few nanometer into two- and three-dimen-

[*] Prof. Dr. H. Weller, C. Pacholski, Dipl.-Ing. A. Kornowski
Institut für Physikalische Chemie
Universität Hamburg
Bundesstrasse 45, 20146 Hamburg (Germany)
Fax: (+49)40-42838-3452
E-mail: weller@chemie.uni-hamburg.de

[**] We thank Philips Analytical and J. Kolny for X-ray diffraction measurements.

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sionally ordered arrays has been reported.^[7] In these experiments, however, self-assembly is mainly driven by the interactions of the organic ligands rather than by the interaction of the particle cores. Contrarily self-assembled "oriented attachment" was only observed for ligand-free nanoparticles.

Recently, rodlike semiconductor and metal nanoparticles have attracted considerable attention. There are, however, only a few examples reported where those nanorods could be prepared in a controllable manner using evaporation or colloido-chemical techniques.^[8–14] Materials such as ZnO, Co, Au, and CdSe were used for the rods. Rod formation requires anisotropic crystal growth which is usually realized when the free surface energies of the various crystallographic planes differ significantly. For wet chemical synthesis Puentes et al. recently showed that this could be realized in the case of CdSe and Co^[15] by using two different surface ligands, which probably bind selectively to the respective surface planes.

We report here the formation of high-quality single crystalline ZnO nanorods which is based on oriented attachment of preformed quasi-spherical ZnO nanoparticles. The growth from individual particles by crystallographically oriented and partially fused dimers and oligomers to almost perfect rods is monitored by high-resolution transmission electron microscopy (TEM) and XRD.

ZnO nanoparticles were prepared from zinc acetate dihydrate in alcoholic solution under basic conditions.^[16] The procedure is a modification of the method developed by Henglein et al.^[17] We found that the shape of the ZnO particles was very sensitive to the overall concentration of precursors. At a zinc acetate dihydrate concentration of below 0.01M quasi-spherical particles were formed, whereas mainly nanorods were formed at 10 times higher concentrations. Similar observations were reported by Vergés et al. for the formation of rodlike microcrystals.^[5]

To learn more about the growth mechanism, we have performed the experiments in a different way. We first prepared a sol of quasi-spherical particles at low concentrations (0.01M, starting sol), increased the particle concentration in a second step by solvent evaporation, and finally refluxed these colloidal solutions for different lengths of time. Rod formation occurred exclusively during the final heating step, that is from already formed quasi-spherical particles. All experiments described in hereafter were performed under these conditions. The particles of the starting sol are depicted in the TEM image in Figure 1 A. An average particle size of approximately 3 nm is seen and it is assumed that faceted crystalline surfaces are already present, but not detectable by high-resolution TEM due to the small size and relatively low contrast of ZnO. The corresponding powder X-ray diffractogram is depicted in Figure 2 (curve A). It exhibits the typical size-broadened reflections from wurtzite-type ZnO. Scherrer line width analysis of all shown peaks yields particle diameters around 3 nm which is consistent with the TEM images. Increasing the particle concentration by a factor of 10 by evaporation of the solvent at room temperature resulted in a particle growth from 3 nm to 5 nm without, however, changing the shape of the particles. The same effect was observed

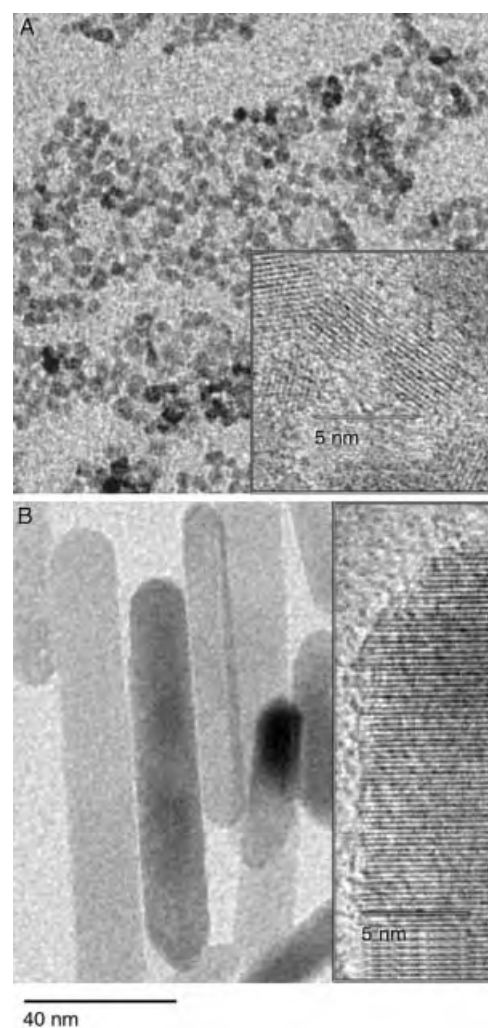


Figure 1. TEM images of ZnO. A) starting sol; B) after one day of reflux of the concentrated sol. The insets show high-resolution TEM images of individual nanoparticles.

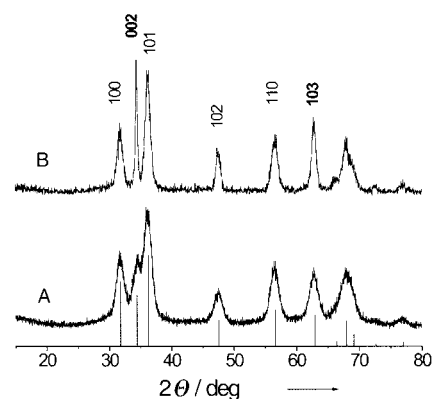


Figure 2. X-ray diffractogram of the ZnO starting sol (A) and after one day of reflux (B).

after reflux of the starting sol for 8 h before the concentration step. Such a gradual growth of quasi-spherical ZnO particles upon aging was also observed and explained by Ostwald ripening.^[18, 19] Refluxing, however, the concentrated solution yields rodlike nanoparticles. An increase in the heating time mainly leads to an increase of the elongation of the particle

along the c axis. After refluxing for one day, single crystalline nanorods with average lengths of 100 nm and widths of approximately 15 nm were formed (Figure 1B).^[20] In the corresponding XRD image (curve B, Figure 2) the 002 reflection has strongly sharpened up which is consistent with rod formation along the c axis. More details about the XRD investigations including solution XRD measurements and simulations are given in the Supporting Information.

Detailed TEM investigations in an early stage of rod formation (reflux for 2 h) are shown in Figure 3. At low magnification (Figure 3A) aggregated quasi-spherical particles are recognized beside already formed short rods. Most of

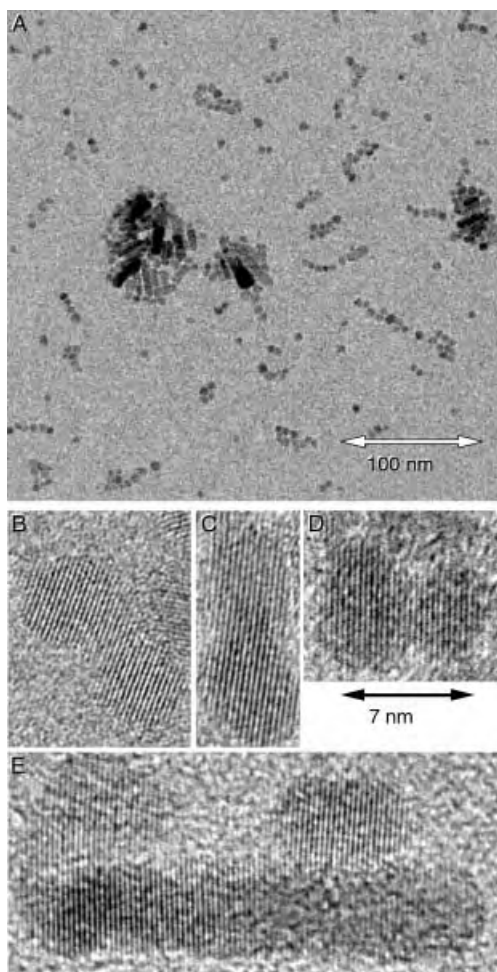


Figure 3. A) TEM image of the concentrated solution after reflux for 2 h; B)–D) high-resolution TEM images of dimers formed by oriented attachment; E) oligomer structure of several nanoparticles fused after oriented attachment.

the aggregated particles form pearl-chain-like structures. High-resolution TEM images of a series of aggregated particles are shown in Figure 3B–D. It is seen that the lattice planes of the depicted particles are almost perfectly aligned. Moreover, one recognizes that the lattice planes go straight through the contact areas, that is the particles are epitaxially fused together; bottlenecks between the adjacent particles are still visible. In the majority of images we see oriented attachment along the c axis (002), but we also find examples

of lateral oriented attachment parallel to the c axis. In some cases one can even observe how the individual particles are aligned like a wall, where the second layer of bricks is just started to be put on the first (Figure 3E). The observed lattice planes in these images are the 002 or 100, which lie perpendicular or parallel to the c axis, respectively. In all images the longest extension of the aggregates is manifested in the direction of the c axis. More examples are shown in the Supporting Information. We do not observe oriented attachment in all aggregated particles. If, however, the particles are fused together, the lattice planes are aligned relative to each other. Thus, oriented attachment seems to be the prerequisite for the condensation step leading to crystallite fusion under our experimental conditions.

This type of oriented attachment implies that the aspect ratio of the rods should peak at integer numbers, at least in an early stage of growth, where the width of the rods is almost identical to the diameter of the particles in the concentrated starting sol. This is indeed observed as shown in the histogram in Figure 4.^[21]

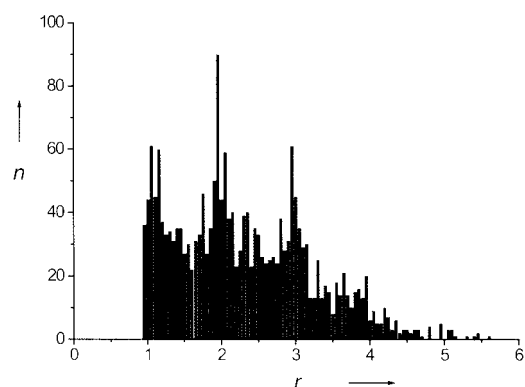


Figure 4. Histogram (with n =frequency) showing the aspect ratio r (length/width) of 2000 ZnO nanorods at an early stage of growth (2 h reflux). The width of the rods at this stage is almost identical to the diameter of the quasi-spherical nanoparticles.

In summary the presented experiments provide strong evidence that oriented attachment of preformed quasi-spherical ZnO nanoparticles is a major reaction path during the formation of single crystalline nanorods under the described conditions. In the finally formed rods the bottlenecks between the adjacent particles must have been filled up and the surfaces parallel to the c axis must somehow have been smoothened. We believe that this occurs by conventional mechanism of dissolution and growth of monomers, which might also result in an overall growth of the rods, especially after long times of reflux. In this sense, Ostwald ripening does not only compete with, but assists the growth process by oriented attachment in order to yield finally high-quality rodlike nanocrystals.

Presently we can only speculate why oriented attachment preferentially occurs along the c axis (although it also happens along other crystal orientations). One reason might arise from the wurtzite structure itself. If complete 002 planes are formed, their reactivity should be different at the bottom and the top of the c axis, since one of these layers is formed by zinc

and the other by oxygen. In alkaline water-containing solutions, this situation will partially be altered by the adsorption of OH^- or H_2O . Zn and O atoms are located in an alternating manner in the 100 planes parallel to the c axis. Thus, hydroxylation and therefore also counterion adsorption should be different. Different amounts of counterions or different surface charges could hinder or favor oriented attachment which requires an intimate contact of the respective surface planes. Also the acetate ions from the precursor salt might act in this sense. A similar role of counterion adsorption is currently also discussed for crystal growth during biomineralization.^[22]

We believe that oxide nanoparticles are very favorable for oriented attachment for two reasons: first, organic ligands, which prevent intimate contact of crystal planes, are usually not needed for stabilization; and second, crystalline fusion of correctly attached particles does not only lead to a gain in lattice-free energy but also in free energy of polycondensation.

The presented growth mechanism offers an excellent tool to design advanced materials with anisotropic materials properties. One application is the inclusion of nanoparticle building blocks with a large number of reactive surfaces—a situation that is already partially realized with the growth of ZnO nanoparticles (cf. Figure 3E). This would open access to the synthesis of more complex crystalline three-dimensional structures in which the branching sites could be added as individual nanoparticles.

Experimental Section

For the preparation of the ZnO nanospheres zinc acetate dihydrate (0.01 M) was dissolved in methanol (125 mL) under vigorous stirring at about 60 °C. Subsequently, a 0.03 M solution of KOH (65 mL) in methanol was added dropwise at 60 °C. The reaction mixture was stirred for 2 h at 60 °C (details see ref. [16]).

The resulting solution (stock solution) was concentrated by evaporation of the solvent and heated for different lengths of time to obtain rod-shaped particles.

Received: January 10, 2002 [Z18502]

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The First “Naked” Primary Phosphanide Anion [ArPH][−]**

Valentyn L. Rudzevich, Heinz Gornitzka, Karinne Miqueu, Jean-Marc Sotiropoulos, Geneviève Pfister-Guillouzo, Vadim D. Romanenko, and Guy Bertrand*

Alkali metal phosphanides are key transfer agents in both main group and transition metal chemistry.^[1] Although these species are normally represented simply as R₂PM or RPHM, they are usually strongly associated in solution and form aggregates in the solid state through the phosphorus centers bridging two or more metal centers.^[2] The structural topology of alkali metal phosphanides is mainly determined by the donor base or coordinating solvent, the radius and polarizability of the metal, and the spatial requirement of the substituents.^[3] Although several conceptual approaches have been developed to prevent intermolecular interactions,^[4] only a few monomeric alkali metal diorganophosphanides are known, and compounds without a metal–phosphorus bond within a contact ion pair remain extremely scarce.^[5] Moreover, despite extensive studies of the alkali metal salts of primary phosphanes, no monomeric structures and no naked monoorganylphosphanides have been described.^[4d,f, 6] Here we report on the use of the bulky electron-withdrawing 2,6-bis(trifluoromethyl)phenyl (Ar_t) substituent^[7] for the preparation of a naked primary phosphanide anion.

A commonly used synthetic strategy for the preparation of lithium phosphanides involves the treatment of primary or secondary phosphanes with *n*-butyllithium.^[1] However, the reaction of organolithium reagents (MeLi and *n*BuLi) with Ar_tPH₂ (**1**) in diethyl ether proceeds in an entirely different manner. A C–P bond is broken, and MePH₂ and *n*BuPH₂ are formed as the only phosphorus-containing products after work-up.^[8] It is likely that the reaction proceeds through a phosphoranide intermediate,^[9] [Ar_tPH₂(R)][−]Li⁺, which subsequently undergoes a P–C bond cleavage. Ab initio calculations^[10] showed the σ_C^{*} orbital of **1** to be 0.3 eV below that of PhPH₂, which readily explains the anomalous reactivity observed.

In contrast, the reaction of the phosphane **1** with one equivalent of KH in THF at −15 °C results in the immediate elimination of H₂ and the formation of a deep red colored solution of potassium phosphanide **2**. The chemical shift of the P atom in **2** (δ_P = −91, ¹J_{PH} = 173 Hz, ⁴J_{PF} = 32 Hz) is significantly deshielded relative to the phosphane precursor **1** (δ_P = −140, ¹J_{PH} = 216 Hz, ⁴J_{PF} = 28 Hz). A further deshielding of the ³¹P NMR signal (δ_P = −73, ¹J_{PH} = 163 Hz, ⁴J_{PF} = 32 Hz) was observed by addition of one equivalent of [18]crown-6 to a solution of **2** in THF. This result is in sharp contrast to the results observed in the case of the lithium and potassium salts of MesPH₂ (Mes = 2,4,6-trimethylphenyl) for which no difference in the ³¹P chemical shift was observed on addition of crown ethers.^[6b] Red/orange crystals suitable for an X-ray crystallographic study were isolated from a mixture of toluene and THF (4:1) at −10 °C. The salt crystallizes as discrete units of formula [K([18]crown-6)(Ar_tPH)] **3**, with no close intermolecular contacts (Figure 1).^[11] The phosphorus atom is

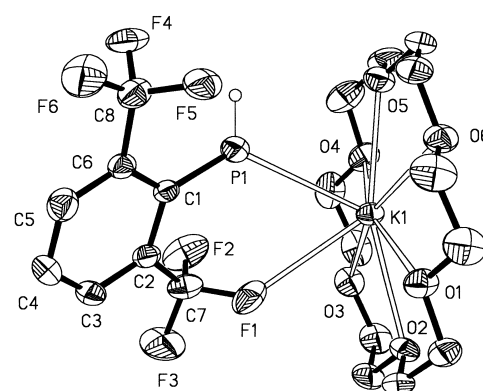


Figure 1. Molecular structure of [K([18]crown-6)(Ar_tPH)] (**3**). Selected bond lengths [pm] and angles [°]: P1–C1 179.4(9), C1–C2 145.2(7), C2–C3 139.3(7), C3–C4 139.1(6), C4–C5 138.9(7), C5–C6 139.8(7), P1–K1 329.3(2), F1–K1 311.0(1); P1–C1–C2 120.1(2), P1–C1–C6 127.0(3), C2–C1–C6 112.9(3), C3–C4–C5 118.3(3).

three-coordinate and adopts a distinctly trigonal-pyramidal configuration (sum of angles around the phosphorus atom: 345.8°). The P–K distance (329.3 pm) is comparable to those found in structurally characterized oligomeric potassium phosphanides.^[6c,d] The potassium cation, in addition to being associated with the P1 atom, is encapsulated by six oxygen atoms of the crown ether, and probably interacts with one fluorine atom (K–F: 311.0 pm).^[12] A significant participation of the Ar_t substituent in the delocalization of the negative charge is indicated by the relatively short P1–C1 bond (179.5 pm).

To effect complete separation of the metal cation and phosphanide anion, two equivalents of [15]crown-5, which is known to form sandwich complexes with potassium cations, were added to a solution of Ar_tPHK in THF that was generated in situ from Ar_tPH₂ and KH. Recrystallization of the resulting precipitate from THF at −20 °C afforded extremely air and moisture sensitive deep red crystals of [K([15]crown-5)₂][Ar_tPH] **4**. Analysis by X-ray diffraction reveals that complexation of the potassium cation by two molecules of [15]crown-5 indeed occurs, thus leaving the

[*] Prof. G. Bertrand, Dr. V. D. Romanenko
UCR-CNRS Joint Research Chemistry Laboratory, UMR 2282
Department of Chemistry, University of California
Riverside, CA 92521-0403 (USA)
Fax: (+1) 909-787-2725
E-mail: gbertran@mail.ucr.edu

Dr. V. L. Rudzevich, Dr. H. Gornitzka
Laboratoire d'Hétérochimie Fondamentale et Appliquée, UMR 5069,
Université Paul Sabatier

118, route de Narbonne, 31062 Toulouse cedex 04 (France)
Dr. K. Miqueu, Dr. J.-M. Sotiropoulos, Dr. G. Pfister-Guillouzo
Laboratoire de Physico-Chimie Moléculaire, UMR 5624
Université de Pau & des Pays de l'Adour
Avenue de l'université, 64000 Pau (France)

[**] Financial support of this work by the CNRS and UCR is gratefully acknowledged. We also thank the Institute du Développement de Ressources en Informatique Scientifique (IDRIS, Orsay), administered by the CNRS, for the calculation facilities and the Université Paul Sabatier for a grant to V.L.R.

phosphorus atom dicoordinate (Figure 2).^[11] Note, that the H atom bonded to the phosphorus atom has been located experimentally, and the observed planar structure was calculated to be around 17 kcal mol⁻¹ lower in energy than the

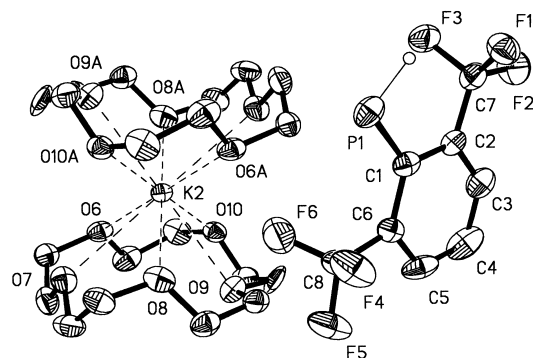
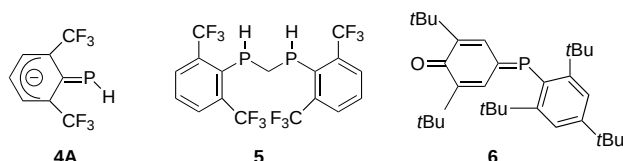


Figure 2. Molecular structure of $[K([15]crown-5)]_2[ArPH]$ (**4**). There are two half molecules of the cationic part in the asymmetric unit, but for clarity only one cation is shown in its full environment. Selected bond lengths [pm] and angles $^\circ$: P1–C1 179.3(6), C1–C6 143.2(7), C1–C2 143.9(7), C2–C3 139.5(8), C3–C4 137.6(8), C4–C5 137.8(8), C5–C6 139.0(8); P1–C1–C2 123.8(4), P1–C1–C6 122.8(4), C2–C1–C6 113.3(5), C1–C2–C3 121.8(5), C3–C4–C5 118.4(6), C4–C5–C6 120.9(6), C5–C6–C1 123.4(6).

structure containing the P–H bond orthogonal to the benzene ring. The P1–C1 bond (179.3 pm) in **4** is half way between that observed for the P–C single bond in the diphosphanomethane **5** (186.9 pm)^[13] and the P=C bond in the phosphaquione **6** (170.5 pm).^[14] The benzene ring in **4** exhibits an even stronger



distortion than in **3**: the C1–C2 (143.9 pm) and C1–C6 (143.2 pm) bonds are significantly longer than the other C–C bonds in the benzene ring (137.6–139.5 pm). These data clearly indicate a delocalization of the negative charge over the ring (**4A**), as confirmed by calculations that found only a small negative charge (–0.32) at the phosphorus atom.^[15]

The ³¹P NMR signal for complex **4** in THF at room temperature is only slightly deshielded ($\delta_P = -67$) compared to that for **3** and appeared as a doublet of septets ($J_{PH} = 163$ Hz, $J_{PF} = 32$ Hz), which indicates the magnetic equivalence of the CF₃ groups. However, the ¹⁹F NMR signal ($\delta_F = +10$) is broad, which suggests a dynamic phenomenon. The CF₃ groups become magnetically nonequivalent, as evident by the observation of two broad ¹⁹F signals at –20 °C. Decreasing the temperature to –50 °C gave well-resolved multinuclear NMR spectra, which clearly supports structure **4A**.^[16] For example, the ³¹P{¹H} NMR signal obtained at –50 °C is a quartet of quartets ($J_{PF} = 72$ and 9 Hz), and the six ring carbon atoms are different: the *para* carbon atom is at very high field ($\delta_C = 105.9$) and the *ipso* carbon atom at very low field ($\delta_C = 170.3$), which is in the range expected for phosphalkenes.

The existence of the naked phosphanide **4**, both in the solid state and in solution, is in line with the calculated high gas-phase acidity of Ar₂PH₂ (1410 kJ mol⁻¹), compared to those of PhPH₂ (1475 kJ mol⁻¹) and PH₃ (calcd: 1524, expt.: 1549 kJ mol⁻¹).^[17] In fact, the gas-phase acidity of Ar₂PH₂ is comparable to that of HCO₂H (calcd: 1401, expt.: 1442 kJ mol⁻¹).^[17]

Experimental Section

All reactions and manipulations were carried out in an atmosphere of dry argon by using standard Schlenk procedures or a glove box. Solvents were distilled over Na/K alloy. 2,6-Bis(trifluoromethyl)phenyldichlorophosphane was prepared according to a known procedure.^[18]

1: A solution of Ar₂PCl₂ (13.1 g, 41.5 mmol) in diethyl ether (25 mL) was added dropwise at –60 °C to a stirred suspension of LiAlH₄ (3.1 g, 82.9 mmol) in diethyl ether (55 mL). After the addition was complete, stirring was continued for 1 h at –60 °C, for 2 h at –30 °C, and for 10 h at room temperature. The solution was then cooled to –30 °C and a 20% aqueous solution of NH₄Cl (20 mL) slowly added. The organic layer was separated, the aqueous phase then treated with 40 mL of a 30% aqueous solution of NaOH and extracted immediately with diethyl ether (100 mL). The combined organic phases were dried with sodium sulfate and **1** purified by distillation: b.p. 31–32 °C/0.5 torr (63% yield).

3: A solution of **1** (337 mg, 1.37 mmol) in THF (1 mL) was added to a suspension of KH (55 mg, 1.37 mmol) in THF (3 mL) at –15 °C. The orange solution was stirred for 30 min and then treated with [18]crown-6 (362 mg, 1.37 mmol). After evaporation of the solvent, **3** was recrystallized from a mixture of toluene and THF (4:1; 75% yield).

4: Potassium phosphanide was treated with two equivalents of [15]crown-5 in a similar procedure as for **3**. After recrystallization from THF, **4** was isolated as deep red crystals (83% yield).

Received: July 23, 2001

Revised: January 24, 2002 [Z17570]

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- [11] Crystal data for **3** and **4**: **3**: $\text{C}_{20}\text{H}_{28}\text{F}_6\text{KO}_6\text{P}$, $M_r = 548.49$, monoclinic, space group $P2_1/n$, $a = 10.44(6)$, $b = 17.38(8)$, $c = 14.53(13)$ Å, $\beta = 94.4(3)^\circ$, $V = 2629(30)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.386 \text{ Mg m}^{-3}$, $F(000) = 1136$, $\lambda = 0.71073$ Å, $T = 193(2)$ K, $\mu(\text{MoK}\alpha) = 0.337 \text{ mm}^{-1}$, crystal size $0.1 \times 0.4 \times 0.7 \text{ mm}^3$, $1.83 \leq \theta \leq 26.37^\circ$, 15 730 reflections (5367 independent, $R_{\text{int}} = 0.0358$), $T_{\text{min}} = 0.825186$, $T_{\text{max}} = 1.0$, 311 parameters, $R1$ [$I > 2\sigma(I)$] = 0.0424, $wR2$ (all data) = 0.0985, max. residual electron density: 0.423 e Å^{-3} . **4**: $\text{C}_{28}\text{H}_{44}\text{F}_6\text{KO}_{10}\text{P}$, $M_r = 724.70$, monoclinic, space group $P2_1/c$, $a = 11.964(2)$, $b = 12.251(2)$, $c = 23.154(3)$ Å, $\beta = 96.195(3)^\circ$, $V = 3374.0(8)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.427 \text{ Mg m}^{-3}$, $F(000) = 1520$, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $\mu(\text{MoK}\alpha) = 0.290 \text{ mm}^{-1}$, crystal size $0.01 \times 0.5 \times 0.6 \text{ mm}^3$, $1.71 \leq \theta \leq 21.97^\circ$, 13 038 reflections (4108 independent, $R_{\text{int}} = 0.0798$), $T_{\text{min}} = 0.749166$, $T_{\text{max}} = 1.000000$, 4108 parameters, 440 restraints, $R1$ [$I > 2\sigma(I)$] = 0.0599, $wR2$ (all data) = 0.1424, max. residual electron density: 0.529 e Å^{-3} . Data for both structures were collected at low temperature using oil-coated shock-cooled crystals on a Bruker-AXS CCD 1000 diffractometer. Semi-empirical absorption corrections were employed.^[23] The structures were solved by direct methods (SHELXS-97)^[24] and refined using the least-squares method on F^2 .^[25] CCDC-166948 (**3**) and -166949 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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Cation-Promoted Hierarchical Formation of Supramolecular Assemblies of Self-Organized Helical Molecular Components**

Anne Petitjean, Louis A. Cuccia, Jean-Marie Lehn,*
Hélène Nierengarten, and Marc Schmutz

Helical conformations of organic and inorganic entities have received much attention as a result of their occurrence in many biological systems. Maintained by multiple hydrogen bonds and electrostatic interactions, α -helices are involved in

[*] Prof. Dr. J.-M. Lehn, A. Petitjean, Dr. L. A. Cuccia
Laboratoire de Chimie Supramoléculaire, ISIS-ULP
4 rue Blaise Pascal, 67000 Strasbourg (France)
Fax: (+33) 390-24-11-17
E-mail: lehn@chimie.u-strasbg.fr

Dr. H. Nierengarten
Laboratoire de Spectrométrie
de Masse Bio-Organique, ECPM
25 rue Becquerel, 67000 Strasbourg (France)

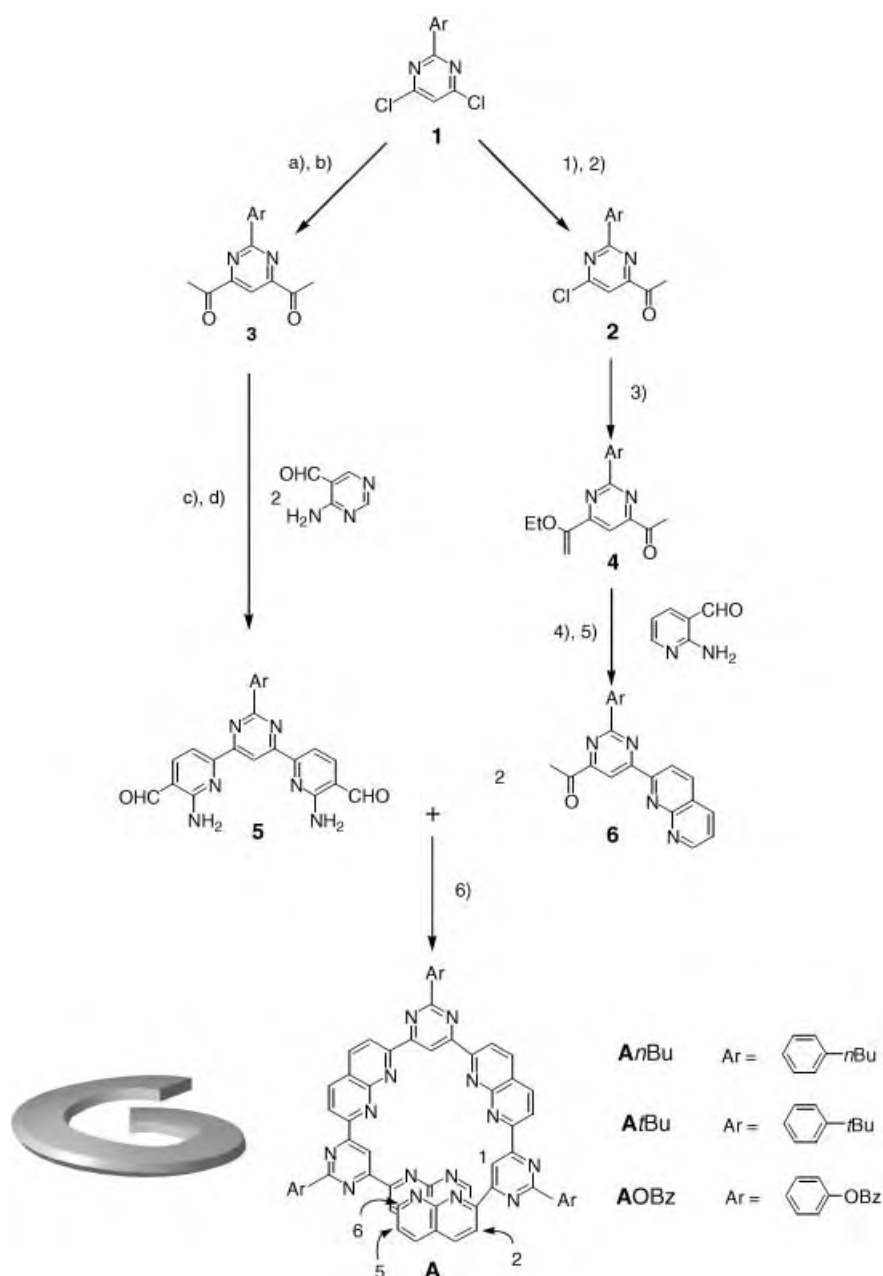
Dr. M. Schmutz
Institut de Génétique et de Biologie Moléculaire et Cellulaire, CNRS/
INSERM/ULP
BP 163, 67404 Illkirch (France)

[**] Dr. R. P. Thummel is thanked for providing helpful advice for the preparation of 4-aminopyrimidine-5-carboxaldehyde. We are indebted to Dr. André Mathis (Institut Charles Sadron) for his kind help with powder diffraction studies. This work was supported by the French "Ministère de la Recherche et de la Technologie". L.A.C. thanks the Collège de France and the CNRS for post-doctoral fellowships. M.S. acknowledges the financial support of INSERM, CNRS, and HUS.

numerous natural architectures, such as ion channels^[1] and pumps,^[2] which require highly ordered subunits. Likewise, in artificial systems, self-organization into a helical spatial arrangement may be induced through hydrogen bonding,^[3] steric interactions,^[4] solvophobic effects,^[5a,b] cation binding,^[5c] and/or local conformational preferences.^[6] In particular, helicity codons based on specially designed sequences of heterocyclic units enforce the self-organization of linear molecular strands into multiturn helical entities.^[7] As a consequence of the primary helix encoding, the preferred conformer may present further specific interactions and undergo a second level, hierarchical self-assembly^[7c, 8, 9] to form polymolecular assemblies. This process may be induced by association with a substrate.^[3d, 10]

Of particular interest is the potential ability of such helically wrapped species to present functional properties such as ion binding and possibly channel-like ion conduction. To this end, the central void must have a diameter sufficient for the inclusion of metallic or organic cations. Replacement of the pyridine group in the previously described pyridine–pyrimidine (py–pym) helicity codon^[7] by 1,8-naphthyridine (napy) should provide such an increase in size. Herein we describe a new type of oligomeric strand composed of alternating pym and napy heterocycles (**A**, Scheme 1), where the interheterocyclic *transoid* conformational preference of 2,2'-bipyridine-like units may be expected to enforce helix formation.^[7] In view of the large dipole moment of napy (4.1 D in benzene, 25 °C),^[11] the helical entity **A** should present a very polar interior and be able to bind a variety of cationic species, which themselves could thereafter promote helix aggregation. Acyclic and macrocyclic structures containing rigidly maintained napy units have been described and found to bind guanidinium ions.^[12]

A series of molecular strands based on napy–pym sequences was synthesized by using the Friedländer methodology (Scheme 1). The 2-aryl-4,6-dichloropyrimidines **1**, which were obtained following published procedures^[13] from commercially available bromo-4-butylbenzenes and 4-hydroxybenzonitrile, were used as starting compounds. Stille coupling of the substituted dichloropyrimidines **1** with 1.1 or 2.1 equivalents of 1-tributylstannylethyl vinyl ether gave respectively the mono- **2** or diacetyl **3** derivative after acidic deprotection of the vinyl ether group. A second Stille coupling on **2** yielded the unsymmetrically protected ketone **4**, which was condensed with 2-aminonicotinaldehyde^[14] and deprotected to give the terminal end **6** of the strands. The



Scheme 1. Synthesis of the polyheterocyclic strands **A**. a) 1-tributylstannylethyl vinyl ether (2.1 equiv), [Pd(PPh₃)₂Cl₂] (0.05 equiv), DMF, 80 °C, 6 h; b) acetone, 2N HCl, room temp., 70 % (two steps); c) 4-aminopyrimidine-5-carboxaldehyde (2.2 equiv), KOH (cat.), EtOH, reflux, 0.5 h; d) 2N HCl in H₂O, reflux, 65 % (two steps). 1) 1-Tributylstannylethyl vinyl ether (1.1 equiv), [Pd(PPh₃)₂Cl₂] (0.03 equiv), DMF, 80 °C, 6 h; 2) acetone, 2N HCl, room temp., 89 % (two steps); 3) 1-tributylstannylethyl vinyl ether (1.1 equiv), [Pd(PPh₃)₂Cl₂] (0.03 equiv), DMF, 80 °C, 6 h, 92 %; 4) 2-aminonicotinaldehyde (1.1 equiv), KOH (cat.), EtOH, reflux 4 h; 5) acetone, 2N HCl, room temp., 84 % (two steps); 6) pyridine, KOH (cat.), reflux, 3 h, 80 %. Bz = benzyl.

diketone **3** was subjected to base-catalyzed condensation with 2.2 equivalents of 4-aminopyrimidine-5-carboxaldehyde, followed by acidic hydrolysis of the terminal pyrimidine to give the compounds **5**. Alkyl- and *O*-benzyl-substituted pyrimidines **5** bearing bis(aminopyridylcarboxaldehyde) were thereby prepared in reasonable yields. The final condensation of **5** and **6** was efficiently performed in pyridine using catalytic amounts of potassium hydroxide and yielded sequences **A** containing four napy and three pym groups. Longer strands were also synthesized by using the same methodology.

On the basis of earlier results involving (py-pym)_n strands,^[7] (napy-pym)_n sequences may be expected to adopt a pre-determined well-defined helical conformation. The presence of such a shape in solution was supported by ¹H NMR spectroscopic studies. The strong upfield shift of the terminal napy protons (up to 0.5 ppm relative to a shorter non-overlapping strand) in the well-resolved and sharp spectrum of **A**/Bu is consistent with overlapping aromatic rings and is diagnostic of the helical folding^[7] represented by structure **A**, which defines an internal cavity with a diameter of about 3.5 Å. This helical arrangement was confirmed by NOE crosspeaks in a ROESY experiment which shows that protons 1 and 2 are close to protons 6 and 5, respectively.

The ¹H NMR spectra of the three helices bearing various substituents in deuterated chloroform showed increased line broadening when the substituent was less bulky (from *t*Bu, to OBz, and to *n*Bu), which is suggestive of intermolecular association at millimolar concentrations. Self-aggregation was confirmed by other experiments: increasing the concentration or the ionic strength of the medium (for example, by addition of NEt₄I in CDCl₃) led to signal shifts indicative of proton shielding (especially for the terminal napy groups). Marked broadening was produced by the addition of a polar solvent such as acetonitrile—a solvophobic aggregation effect reminiscent of solvophobic folding.^[5a,b]

Most interestingly, self-association of helical monomers was strongly influenced by cationic additives. Titrations of the *n*Bu-substituted one-turn helix **A***n*Bu with alkali metal salts (cesium and potassium picrates) showed a strong upfield shift of all the ¹H NMR signals (by approximately 2 ppm) and broadened signals at millimolar concentrations (Figure 1).

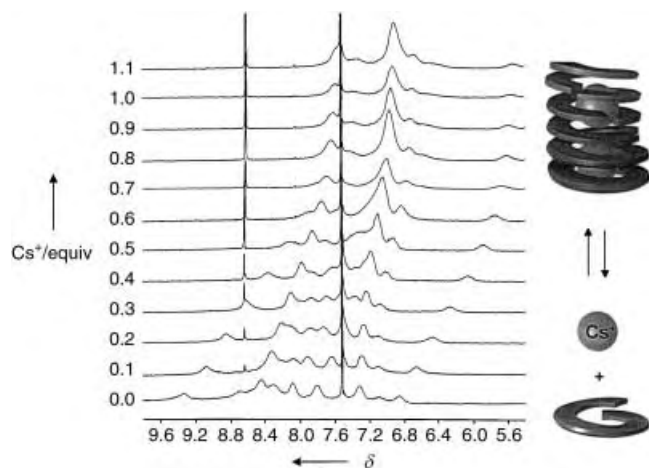


Figure 1. ¹H NMR titration of **A***n*Bu (2.7 mM in CDCl₃/CD₃CN (1.7/1.0)) with cesium picrate (2.9 mM in the same mixture of solvents); right: representation of the formation of a stack of helical **A***n*Bu components containing Cs⁺ ions.

Cations other than alkali ions appear to be even more efficient aggregate inducers, as evident from the line broadening of the NMR signals; indeed, hydronium and guanidinium^[10] ions show stronger effects than the alkali ions. Thus, in a chloroform/ethanol/acetonitrile (3/6/2) mixture, the latter yield birefringent gels, which will be further characterized.

Electrospray mass spectrometry (ES-MS) studies gave results in line with the NMR spectroscopic data. Thus, when a 1/1 mixture of **A***n*Bu and potassium picrate was investigated in the same range of concentrations, mass signals corresponding to assemblies containing *x*–*y* ions for *x* ligands (*y* ≤ *x*) were detected (Figure 2). In addition to potassium ions,

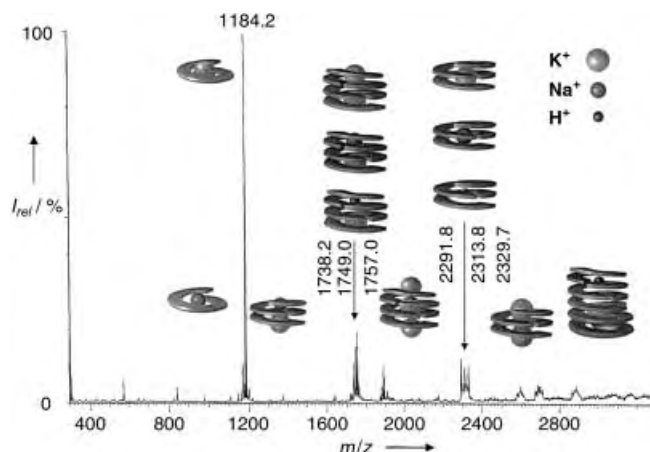


Figure 2. ES-MS spectrum of a 1/1 mixture of **A***n*Bu and potassium picrate (2.7 mM in CHCl₃/CH₃CN (1.7/1.0)), 70 V. *m/z*: 1168.1 [**A**+Na]⁺, 1184.2 [**A**+K]⁺, 1176.4 [2**A**+K+Na]²⁺, 1738.2 [3**A**+K+H]²⁺, 1749.0 [3**A**+K+Na]²⁺, 1757.0 [3**A**+2K]²⁺, 1890.8 [3**A**+3K+Pic]²⁺, 2291.8 [2**A**+H]⁺, 2313.8 [2**A**+Na]⁺, 2329.7 [2**A**+K]⁺, 2597.4 [2**A**+2K+Pic]⁺, 2883.5 [5**A**+K+H]²⁺. The stacked structures shown are speculative, but agree with all the data obtained.

the binding of cesium, sodium, guanidinium ions as well as protons by the supramolecular helix aggregates also occurred. Divalent lead ions (introduced as the triflate salt) formed multiligand assemblies with **A***n*Bu: the ES-MS spectrum of a millimolar solution of the 1/1 complex in CH₃CN/CHCl₃ (1.7/1.0) showed mainly the [3**A**+2Pb]²⁺ adduct. These spectroscopic results agree with the formation of an assembly of stacked helices of component **A** containing cations in the internal void, as schematically represented in Figures 1 and 2.

The formation of a stack-type structure is supported by X-ray powder diffraction patterns, which yield a characteristic distance of 23–26 Å for the assemblies obtained with all the cations, as well as for the ligand itself. This value corresponds to the external diameter of the helix.^[15]

The potassium-containing sample used for the ES-MS studies was investigated by transmission electron microscopy (TEM). Long interdigitated fibers were found (Figure 3), thus confirming by direct observation, the self-association into extended supramolecular assemblies. Single filaments could not be observed under the conditions used for sample preparation because of association. Similar observations were made with cesium ions. No clear textures were observed by TEM in the absence of added cations.

The present results show that the self-organization features resulting from the *transoid* conformational preference of the py–pym units^[7] can be generalized to strands composed of sequences of alternating napy–pym heterocycles as a novel helicity codon, which enforces the formation of a helical

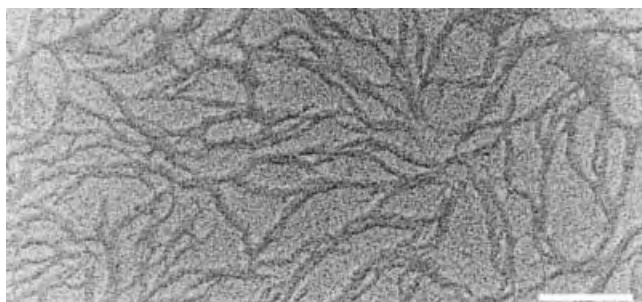


Figure 3. Transmission electron micrograph of a 1/1 mixture of **AnBu** and potassium picrate (3 mM in $\text{CHCl}_3/\text{CH}_3\text{CN}$ (1.7/1.0)). The white bar (bottom right) represents 200 nm. The sample was prepared as described in ref. [3d]).

foldamer^[16] and generates a polar inner void towards the center of which all the napy electrical dipoles are directed. This arrangement induces cation complexation, which in turn promotes the multiple supramolecular association of ligands, through effects such as ion–dipole interaction and π stacking between the aromatic rings.

The hierarchical self-organization observed amounts to a sort of effector-induced growth process and is reminiscent of the self-assembly of the tobacco mosaic virus, where the formation of the helical protein coat results from the induced association of the peptide components by the nucleic acid strand occupying the central void of the polymolecular architecture. The formation of cation-containing polymolecular stacks of helical monomeric components suggests that such entities may potentially act as transmembrane ion channels^[1, 17] that would not only conduct ions but also build up solely if suitable ions are present, thus presenting a most intriguing ability to perform a cation-selective self-regulation of ion flow.

Received: July 2, 2001

Revised: January 23, 2002 [Z17400]

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The Determination of the Absolute Configurations of Diastereomers of (S)-Camphanoyl 3-Hydroxy-5-oxohexanoic Acid Derivatives by X-ray Crystallography**

Kwai-Ming Cheung, Simon J. Coles,
Michael B. Hursthouse, Neil I. Johnson, and
Peter M. Shoolingin–Jordan*

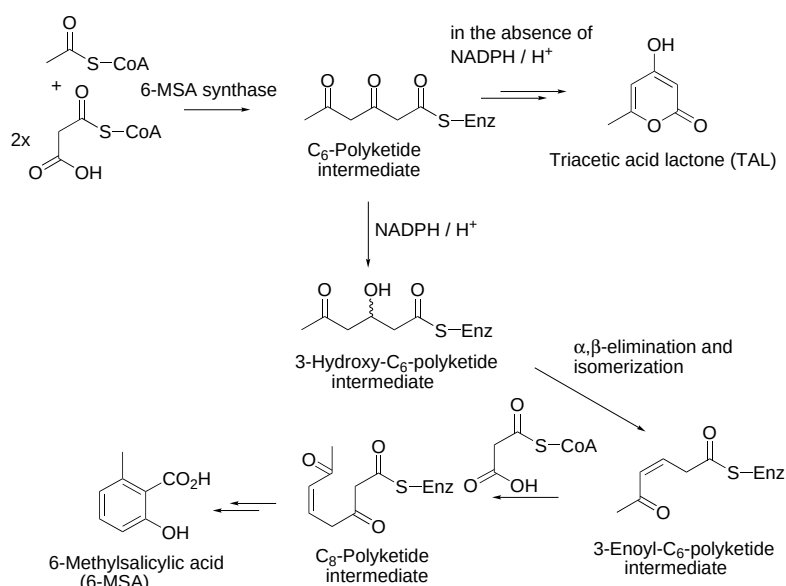
Polyketides form a major class of secondary metabolites,^[1] produced by fungi, lichens, and higher plants. 6-Methylsalicylic acid (6-MSA) is one of the simplest aromatic compounds produced by a polyketide biosynthesis pathway. It is assembled from one molecule of acetyl-coenzyme A (acetyl-CoA),

[*] Prof. P. M. Shoolingin–Jordan, Dr. K.-M. Cheung, Dr. N. I. Johnson
Division of Biochemistry and Molecular Biology
School of Biological Sciences, University of Southampton
Biomedical Sciences Building, Bassett Crescent East
Southampton SO16 7PX (UK)
Fax: (+44) 23-80-594459
E-mail: pmsj@soton.ac.uk

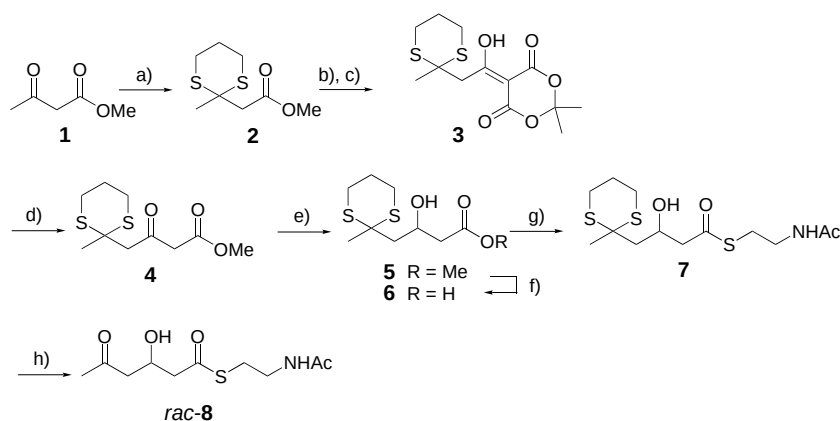
Dr. S. J. Coles, Prof. M. B. Hursthouse
EPSRC National Crystallography Service
Department of Chemistry, University of Southampton
Highfield, Southampton SO17 1BJ (UK)

[**] This work was supported by the EPSRC, the BBSRC, and by the Wellcome Trust. We also thank the Chemical Database Service provided by the EPSRC at Daresbury. We are grateful to Joan Street for providing the NMR service and Dr. J. Langley for the high resolution mass spectroscopy (HRMS) in the Chemistry Department at Southampton.

three molecules of malonyl-CoA, and one molecule of nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), by the enzyme 6-methylsalicylic acid synthase^[2] (Scheme 1). The mechanism of action of this multifunctional enzyme commences with a starter molecule, acetyl-CoA, which undergoes two successive Claisen condensations with two molecules of malonyl-CoA, to form an enzyme-bound C₆-triketide intermediate. This compound is then reduced with NADPH to the corresponding 3-hydroxy-5-oxohexanoyl (3-hydroxy-C₆) intermediate, followed by α,β -elimination and isomerization, to yield a *cis*-5-oxohex-3-enoyl (3-enoyl-C₆) intermediate. A final Claisen condensation with a third malonyl-CoA then occurs, which leads to the production of a C₈ intermediate, which dehydrates and cyclizes to form 6-methylsalicylic acid. In the absence of NADPH, the C₆-triketide intermediate is eliminated from the enzyme and cyclizes prematurely to form triacetic acid lactone (TAL; Scheme 1).^[1] In the presence of NADPH, the resulting hydroxy-C₆ unit is converted through the normal catalytic sequence into 6-MSA. The stereochemical events operating in 6-MSA biosynthesis have been extensively investigated in our laboratory. Specific stereochemical insights were obtained by a series of experiments using chiral (2*R*)[1-¹³C; 2-²H]-malonyl-CoA and (2*S*)[1-¹³C; 2-²H]-malonyl-CoA.^[3] These were incubated with acetyl-CoA, NADPH, and highly purified 6-MSA synthase. The mass spectra of the mixtures were then analyzed and compared. The results of the analysis indicate that there is a single base at the enzyme active site which can perform the α,β -elimination in the 3-hydroxy-C₆ intermediate and the isomerization process in the next step. A key stage in the enzyme reaction is the reduction of the C₆-triketide to the 3-hydroxy C₆ intermediate. A knowledge of the stereochemistry of this hydroxy-intermediate is essential for a full understanding of the mechanism of the reaction pathway. To analyze the role and stereospecificity of the 3-hydroxy-C₆ intermediate and the timing of its formation in the 6-MSA synthase catalytic cycle, it was necessary to develop a synthesis for both chiral 3-hydroxy-C₆ intermediates as their corresponding 2-(acetyl amino)ethyl thioesters (NACs) for incubation these with 6-MSA synthase. There is evidence that NACs are accepted as substrates by some polyketide synthases.^[4] The synthesis of the racemic 2-(acetyl amino)ethyl 3-hydroxy-5-oxohexanethioate (**8**; Scheme 2) has been achieved in our laboratory by protection of the C₅ ketone with a dithiane group. The synthesis of the mixture has also been reported elsewhere using a different method.^[5] Here, we report the resolution of the racemic mixture of **8**, by a method which employs the chiral auxiliary, (*S*)-camphanoyl chloride. Subsequent X-ray crystallographic



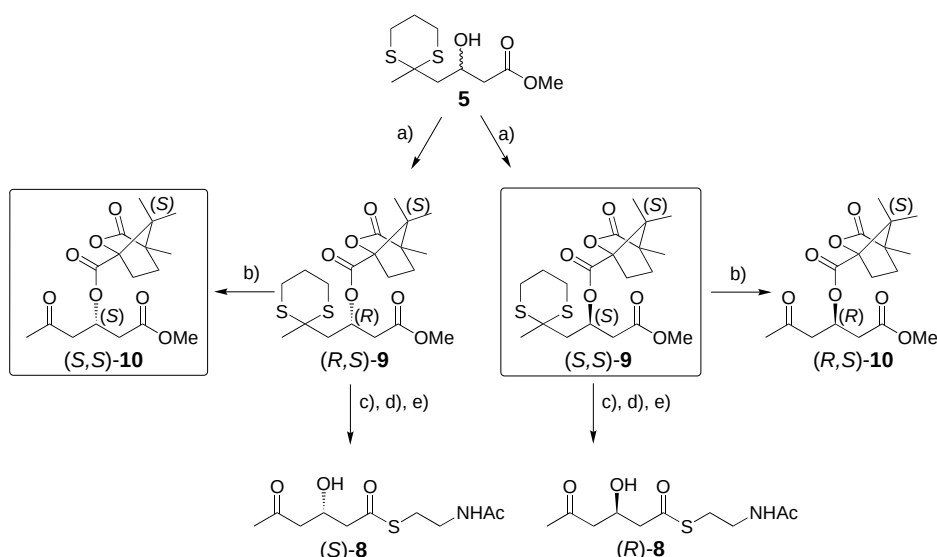
Scheme 1. The biosynthetic pathway for 6-MSA.



Scheme 2. Reagents and conditions: a) ZnCl₂, HCl gas, 1,3-propanedithiol, b) 10 % NaOH, 90 °C/HCl, c) 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), *N,N'*-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), d) MeOH, reflux in toluene, e) NaBH₄, MeOH, f) 2M NaOH/HCl, g) (PhO)₂P(O)(N₃), NEt₃, DMAP, *N*-acetylcysteamine, dimethylformamide (DMF), h) MeI, CaCO₃, 50 °C. Full experimental details and physical data are given in the Supporting Information.

analysis of the corresponding (*S*)-camphanoyl-hydroxy-C₆ derivatives allowed their unambiguous characterization and the assignment of the C3 stereochemistry.

The synthesis of (*S*)-camphanoyl-hydroxy-C₆ derivatives is shown in Scheme 3. A racemic mixture of **5**, which contains the C₆ backbone, was prepared from 2-methyl-[1,3]dithian-2-yl-acetic acid (**2**)^[6] and Meldrum's acid, heated under reflux with methanol in toluene and reduced using NaBH₄. Diastereomers methyl (3*R*)- or (3*S*)-[3-(*S*)-camphanoyloxy]-4-(2-methyl-1,3-dithian-2-yl)butanoate ((*R,S*)-**9** and (*S,S*)-**9**, respectively), were prepared in 45 % yield in a ratio of 1:1, by the reaction of the racemic **5** with (*S*)-camphanoyl chloride. The *RS* and *SS* compounds were separated by column chromatography and recrystallized from toluene. Deprotection, achieved by use of trimethyloxonium tetrafluoroborate,^[7] afforded the corresponding *keto*-derivatives, methyl (3*S*)- or (3*R*)-[3-(*S*)-camphanoyloxy]-5-oxohexanoate,((*S,S*)-



Scheme 3. Reagents and conditions: a) (*S*)-camphanoyl chloride, NEt₃, DMAP, 1,2-dichloroethane (DCE), b) Me₃O⁺BF₄⁻, dichloromethane (DCM), c) 3.5 M HCl/2 M NaOH, HCl, d) (PhO)₂P(O)(N₃), *N*-acetylcysteamine, DMF, e) MeI, CaCO₃, 50 °C^[8]. The boxed structures have been determined by X-ray crystallography.

10 and (*R,S*)-10, respectively),^[8] which were also recrystallized from toluene, each in approximately 85 % yield.

The X-ray crystal structures of (*S,S*)-9 (Figure 1) and (*S,S*)-10 (Figure 2) indicate unambiguously that the syntheses of both the *RS* and *SS* diastereomers were successful. Importantly, the X-ray structures confirm that no loss of chirality occurred at C-3 during deprotection. *R*-8 and *S*-8 were finally obtained by acid and base hydrolyses, and subsequent deprotection.

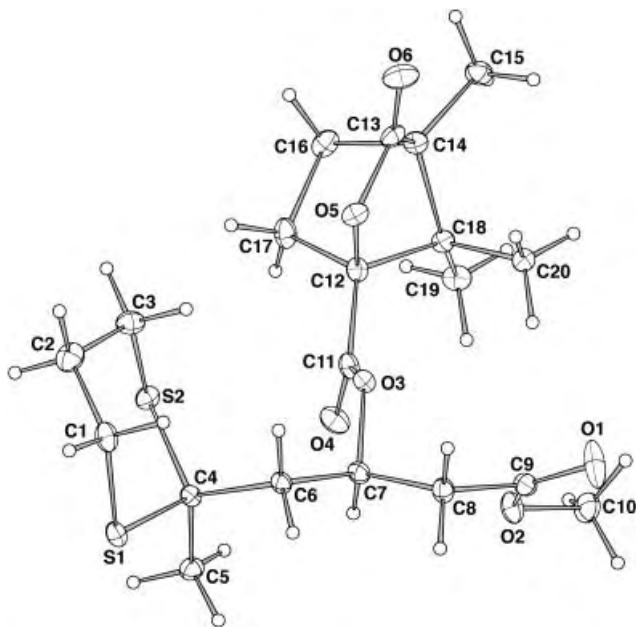


Figure 1. The X-ray crystallographic structure of (*S,S*)-9.

Incorporation experiments were carried out with *R*-8 and *S*-8, using highly purified 6-methylsalicylic acid synthase, isolated from *Penicillium patulum*, to ascertain whether either could be enzymatically transformed into 6-MSA. This would

require the initial transfer of the acyl group to an enzyme thiol, to form a bound 3-hydroxy C₆-intermediate (Scheme 1), followed by dehydration and addition of a malonyl moiety from malonyl-CoA. On incubation with the enzyme, neither intermediate was able to form 6-MSA at a rate significantly greater than that with malonyl-CoA alone, although the enzyme was inhibited by both enantiomers. This result could be predicted, as the natural substrates of 6-MSA synthase are CoA thioesters rather than *N*-acetylcysteamine thioesters. Furthermore, observations with other polymerases suggest that such enzymes do not always recognize externally added intermediates or their analogues. For instance, in the tetra-

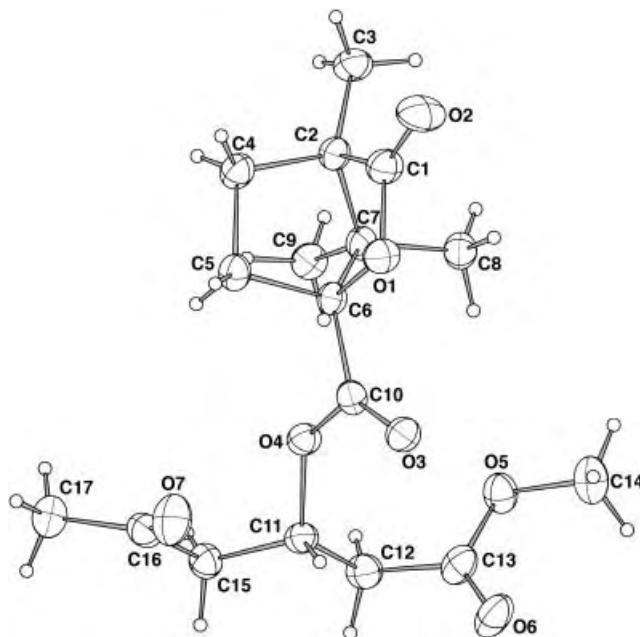


Figure 2. The X-ray crystallographic structure of (*S,S*)-10.

merization reaction catalyzed by porphobilinogen deaminase, neither dipyrromethanes^[9] nor tripyrranes^[10] are able to act as substrates, despite their known involvement as enzyme bound species.^[11] Thus, the enzyme recognizes only the monopyrrolic building unit, porphobilinogen, rather than more advanced intermediates. A similar observation has been made in fatty acid biosynthesis, in which advanced intermediate thiol esters are not recognized by the enzyme and are not incorporated into palmitic acid.^[12] Whilst these results are somewhat disappointing with respect to determination of the absolute stereochemistry of enzyme bound 3-hydroxy-5-oxohexanoyl thiolester intermediate, the synthetic methodology devel-

oped, and the availability of the two enantiomers, will be useful for investigating other polyketide synthases, some of which can recognize *N*-acetylcysteamine thiol esters.

Experimental Section

3: Compound **2** (3.0 g, 15.6 mmol), Meldrum's acid (2.47 g, 17.1 mmol), and DMAP (2.86 g, 23.4 mmol) were dissolved in CH_2Cl_2 (100 mL). The solution was cooled to -5°C and a solution of DCC (3.55 g, 17.2 mmol) in CH_2Cl_2 (50 mL) was added dropwise over an hour. The resulting solution was stirred at 4°C for 18 h, during which time crystals of dicyclohexylurea were formed. After filtration, the organic solution was washed with 5% KHSO_4 , brine, and water, and dried over Na_2SO_4 . After filtration and evaporation of the solvent, crystals were obtained (4.5 g). The crystals were recrystallized from *n*-hexane, filtered when hot. Pale yellow crystals were collected (4.2 g, 85%). M.p. = $92-93^\circ\text{C}$; IR (Nujol): $\tilde{\nu}$ = 2950, 1755, 1670, 1575, 1210, 1140 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 15.35 (s, 1H; OH), 4.00 (s, 2H; CH_2), 3.15 (m, 2H; CH_2), 2.70 (m, 2H; CH_2), 2.15 (m, 2H; CH_2), 1.79 (s, 6H; $2 \times \text{CH}_3$), 1.75 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 191.6, 160.9, 104.9, 94.0, 48.3, 44.3, 29.5, 27.3, 26.8, 24.5; δ_{DEPT} : [CH_3] 29.5 and 26.8. [CH_2] 44.3, 27.3 and 24.5; ES-MS +ve mode: [$M^+ - \text{H}$] 317.0 (84), 212.5 (10); HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{S}_2\text{O}_5$: 318.0596, found: 318.0598.

4: Compound **3** (1.2 g, 3.8 mmol) and MeOH (0.6 g, 18.8 mmol) were mixed in dry toluene (20 mL), and the resulting solution was heated under reflux for 3 h. After the evaporation of the solvent, a yellow oil was obtained (0.73 g, 77%). The ratio of the keto to enol forms was about 3.7:1. IR (liquid film): $\tilde{\nu}$ = 2980, 2950, 1760, 1732, 1670, 1640, 1250, 1030 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): [keto] δ = 3.76 (s, 3H; CH_3), 3.62 (s, 2H; CH_2), 3.24 (s, 2H; CH_2), 2.80–3.05 (m, 4H; $2 \times \text{CH}_2$), 1.90–2.15 (m, 2H; CH_2) and 1.75 (s, 3H; CH_3); [enol] δ = 12.05 (s, 1H; OH), 5.11 (s, 1H; CH), 3.75 (s, 3H; CH_3), 3.24 (s, 2H; CH_2), 2.80–3.05 (m, 4H; $\text{CH}_2 + \text{CH}_2$), 1.90–2.15 (m, 2H; CH_2), and 1.75 (s, 3H; CH_3); HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{S}_2\text{O}_3$: 248.0541, found: 248.0539.

5: Compound **4** (2.58 g, 10.4 mmol) was dissolved in MeOH (40 mL) and the solution was cooled to 0°C . NaBH_4 (1.18 g, 31.0 mmol) was added in portions over 15 min and the resulting solution was stirred at 25°C for an hour. Saturated citric acid was added, and the solution was extracted with ether. The combined ether layers were washed with water and dried over Na_2SO_4 . After evaporation of the solvent, a yellow oil was obtained (2.05 g, 79%). IR (LF): $\tilde{\nu}$ = 3520, 2990, 2950, 1745, 1180, 1010 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 4.38 (m, 1H; CH), 3.65 (s, 3H; CH_3), 3.64 (d, J = 3.8 Hz, 1H; OH), 3.00 (m, 2H; CH_2), 2.80 (m, 2H; CH_2), 2.57 (dd, J = 15.4 and 7.7 Hz, 1H; CH), 2.52 (dd, J = 15.4 and 5.2 Hz, 1H; CH), 2.38 (dd, J = 15.0 and 8.8 Hz, 2H; CH_2), 1.85–2.10 (m, 2H; CH_2), and 1.64 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 172.2, 65.7, 51.8, 47.5, 46.7, 42.1, 28.4, 26.8, 26.6 and 24.6; HRMS calcd for $\text{C}_{10}\text{H}_{18}\text{S}_2\text{O}_3$: 250.0697, found: 250.0695.

6: The ester **5** was stirred in 2 M NaOH for 18 h at 25°C , and 2 M HCl was added until pH 4–5 was reached. The solution was extracted with ether. After the work-up, a yellow oil was obtained in approximately 70% yield. IR (LF): $\tilde{\nu}$ = 3450, 3000–2500, 2990, 2960, 1725, 1190, 1100 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 4.42 (m, 1H; CH), 3.02 (m, 2H; CH_2), 2.80 (m, 2H; CH_2), 2.62 (dd, J = 15.8 and 7.4 Hz, 1H; CH), 2.54 (dd, J = 15.8 and 5.5 Hz, 1H; CH), 2.47 (2H, dd, J = 15.0 and 9.5 Hz), 1.85–2.15 (2H, m), and 1.70 (3H, s).

7: Compound **6** (0.28 g, 1.2 mmol), diphenylphosphoryl azide (0.65 g, 2.4 mmol), NEt_3 (0.14 g, 1.4 mmol) and a catalytic amount of DMAP were dissolved in DMF (8 mL), and the solution was stirred at 25°C under N_2 for 3 h. A solution of *N*-acetylcysteamine (0.42 g, 3.5 mmol) and NEt_3 (0.36 g, 3.6 mmol) in DMF (3 mL), prepared under N_2 , was added through a syringe. The solution was stirred at 25°C for 24 h under N_2 . The DMF was then diluted with brine (10 mL) and extracted with ether. The combined ether layers were dried over Na_2SO_4 , filtered and evaporated, yielding a yellow oil (0.46 g). The oil was chromatographed in EtOAc : petroleum ether (40–60 $^\circ\text{C}$) (1:2), and purified again by preparative TLC (thin-layer chromatography) with EtOAc:MeOH (5:1). A light yellow oil (0.16 g, 40%) was obtained. R_f = 0.65 (EtOAc:MeOH (5:1)); IR (LF): $\tilde{\nu}$ = 3350, 3120, 2960, 1670, 1560, 1300, 1120, 760 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 ,

25°C): δ = 6.00 (s, broad, 1H; NH), 4.45 (m, 1H; CH), 3.75 (s, 1H; OH), 3.45 (m, 2H; CH_2), 3.08 (m, 2H; CH_2), 2.75–3.05 (m, 4H; $2 \times \text{CH}_2$), 2.68 (dd, J = 15.0 and 9.0 Hz, 1H; CH), 2.40 (dd, J = 15.0 and 4.4 Hz, 1H; CH), 2.05 (m, 2H; CH_2), 1.90 (m, 2H; CH_2), 1.98 (s, 3H; CH_3) and 1.70 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 198.0, 170.4, 66.3, 51.5, 47.3, 46.6, 39.4, 28.8, 28.4, 26.8, 26.6, 24.5 and 23.2; δ_{DEPT} (CDCl_3): [CH , CH_3] 66.3, 28.4 and 23.2. [CH_2] 51.5, 46.6, 39.4, 28.8, 26.8, 26.6 and 24.5; ES-MS +ve mode: [$M^+ + \text{Na}$] 359.5 (91), 238.9 (62), 117.7 (100). HRMS calcd for $\text{C}_{13}\text{H}_{23}\text{NS}_2\text{O}_3$: 337.0840, found: 338.0740 ($M^+ + \text{H}$).

rac-8: Compound **7** (35 mg, 0.1 mmol), CH_3I (200 μL) and CaCO_3 (20 mg) were mixed and stirred in $\text{CH}_3\text{CN}:\text{H}_2\text{O}:\text{O}_2$ (2 mL) at 50°C . The reaction was monitored at half hourly intervals by TLC. Additional portions of $\text{CH}_3\text{I}/\text{CaCO}_3$ were added to the reaction suspension until the disappearance of the starting material was confirmed by TLC. Four additional portions of $\text{CH}_3\text{I}/\text{CaCO}_3$ were added in total. The solvents were subsequently evaporated and the oil was dried in vacuo. CH_2Cl_2 was added to the residue and filtered. After the TLC separation, a light yellow oil was obtained (11.8 mg, 46%). R_f = 0.53 (EtOAc:MeOH (5:1)); IR (LF): $\tilde{\nu}$ = 3400, 2950, 1710, 1690, 1660, 1550, 1380, 1300 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 5.82 (s, 1H; NH), 4.54 (m, 1H; CH), 3.46 (m, 2H; CH_2), 3.38 (d, J = 3.7 Hz, 1H; OH), 3.07 (t, J = 6.3 Hz, 2H; CH_2), 2.81 (dd, J = 15 and 7.7 Hz, 1H; CH), 2.73 (dd, J = 15 and 5.2 Hz, 1H; CH), 2.70 (d, J = 5.9 Hz, 2H; CH_2), 2.20 (s, 3H; CH_3), 1.98 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 208.5, 198.1, 170.5, 64.9, 49.9, 48.9, 39.2, 30.8, 28.9, 23.2; δ_{DEPT} (CDCl_3): [CH , CH_3] 64.9, 30.8, 23.2. [CH_2] 49.9, 48.9, 39.2, 28.9; ES-MS +ve mode: [$M^+ + \text{H}$] 247.9 (95), 229.9 (33), 119.6 (100); HRMS calcd for $\text{C}_{10}\text{H}_{17}\text{NSO}_4$: 247.0878, found: 248.0870 [$M^+ + \text{H}$].

(*S,S*)-**9** and (*R,S*)-**9**: To a solution of compound **5** (110 mg, 0.44 mmol), NEt_3 (148 mg, 1.46 mmol), DMAP (54 mg, 0.44 mmol) in DCE (10 mL), (*S*)-camphanoyl chloride (317 mg, 1.46 mmol) in DCE (2 mL) were added and the solution was heated under reflux for 24 h. After cooling, the organic layer was washed with water, sat. NaHCO_3 solution, sat. citric acid, and brine (40 mL of each), and dried over anhydrous Na_2SO_4 . After evaporation of the solvent, an oil (213 mg) was obtained. The diastereomers were separated using a SiO_2 column, eluted with EtOAc: petroleum ether (40–60 $^\circ\text{C}$)/1:2.

(*S,S*)-**9** was obtained as colorless needles (42 mg, 22%) and recrystallized in toluene. M.p. = $116-117^\circ\text{C}$. R_f = 0.59; IR (Nujol): $\tilde{\nu}$ = 2950, 1790, 1752, 1740, 1170, 1115 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 5.53 (m, 1H; CH), 3.68 (s, 3H; CH_3), 2.96 (m, 2H; CH_2), 2.70 (m, 4H; $2 \times \text{CH}_2$), 2.30–2.60 (m, 3H; CH + CH_2), 1.80–2.10 (m, 4H; CH + CH + CH_2), 1.65 (m, 1H; CH), 1.62 (s, 3H; CH_3), 1.09 (s, 3H; CH_3), 1.07 (s, 3H; CH_3), and 0.95 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 178.4, 170.1, 166.9, 90.9, 69.6, 54.9, 54.3, 51.9, 46.9, 43.9, 39.8, 30.7, 28.9, 28.3, 26.8, 24.6, 16.7, 16.5 and 9.7; ES-MS (+ve mode): [$M^+ + \text{Na}$] 453.0 (100), 234.9 (20); HRMS calcd for $\text{C}_{20}\text{H}_{30}\text{O}_6\text{S}_2$: 430.1484; found: 431.1474 [$M^+ + \text{H}$].

(*R,S*)-**9** was obtained as colorless crystals (43.5 mg, 23%). M.p. = $110-111^\circ\text{C}$; R_f = 0.5; IR (Nujol): $\tilde{\nu}$ = 2950, 1800, 1765, 1748, 1185, 1125, 1070 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 5.53 (m, 1H; CH), 3.68 (s, 3H; CH_3), 2.90 (m, 2H; CH_2), 2.75 (m, 4H; $2 \times \text{CH}_2$), 2.30–2.60 (m, 3H; CH + CH_2), 1.85–2.10 (m, 4H; CH + CH + CH_2), 1.65 (m, 1H; CH), 1.62 (s, 3H; CH_3), 1.09 (s, 3H; CH_3), 1.07 (s, 3H; CH_3), and 0.95 (s, 3H; CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): δ = 178.0, 170.1, 166.7, 90.8, 69.8, 54.8, 54.2, 51.9, 46.9, 44.3, 39.7, 31.0, 29.0, 28.4, 26.8, 26.6, 24.7, 16.8, 16.7, 9.6; ES-MS (+ve mode): [$M^+ + \text{Na}$] 453.0 (100), 234.9 (20); HRMS calcd for $\text{C}_{20}\text{H}_{30}\text{O}_6\text{S}_2$: 430.1484; found: 431.1400 [$M^+ + \text{H}$].

(*R,S*)-**10**: Compound (*S,S*)-**9** (18 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (4 mL), trimethoxyoxonium tetrafluoroborate (36.5 mg, 0.25 mmol) was added and the resulting suspension was stirred vigorously at room temperature. The reaction was monitored by TLC. After one hour, water (4 mL) was added and the cloudy solution was stirred for a further 15 min. The organic layer was washed with water (2×10 mL) and dried over anhydrous Na_2SO_4 . After evaporation of the solvent, the crude product was purified by preparative TLC (SiO_2) in EtOAc:petroleum ether (40–60 $^\circ\text{C}$) (1:2). Colorless crystals (12 mg, 84.3%) were obtained. M.p. = $60-61^\circ\text{C}$. R_f = 0.19; IR (Nujol): $\tilde{\nu}$ = 2940, 1800, 1765 (s, broad), 1730, 1190, 1165, 1125, 1080, 950 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25°C): δ = 5.70 (m, 1H; CH), 3.68 (s, 3H; CH_3), 2.98 (dd, J = 17.3 and 7 Hz, 1H; CH), 2.86 (dd, J = 17.3 and 6.3 Hz, 1H; CH), 2.77 (dd, J = 15.8 and 5.5 Hz, 1H; CH), 2.70 (dd, J = 15.8 and 7 Hz, 1H; CH), 2.42 (m, 1H; CH), 2.20 (s, 3H; CH_3), 1.95 (m,

2H; CH₂), 1.68 (m, 1H; CH), 1.10 (s, 3H; CH₃), 1.05 (s, 3H; CH₃), and 0.95 (s, 3H; CH₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 204.5, 178.2, 170.1, 166.6, 90.9, 67.9, 54.9, 54.3, 51.9, 46.6, 38.1, 30.7, 30.5, 28.9, 16.6, 16.4 and 9.7; ES-MS (+ve mode): [M⁺+Na] 363.2 (100), 283.5 (18), 239.1 (20); HRMS calcd for C₁₇H₂₄O₇: 340.1522, found: 341.1580 [M⁺+H].

(*S,S*)-**10**: The preparation of this compound is as described for (*R,S*)-**10**. Starting material (*R,S*)-**9** (13.3 mg, 0.03 mmol) was used and the product was obtained as colorless crystals (9 mg, 85.6%). M.p. = 92–93 °C; *R*_f = 0.19; IR (Nujol): $\tilde{\nu}$ = 2940, 1810, 1755 (s, broad), 1722, 1190, 1164, 1120, 950 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 5.70 (m, 1H; CH), 3.69 (s, 3H; CH₃), 2.98 (dd, *J* = 17.3 and 7 Hz, 1H; CH), 2.86 (dd, *J* = 17.3 and 5.5 Hz, 1H; CH), 2.77 (dd, *J* = 15.8 and 5.5 Hz, 1H; CH), 2.70 (dd, *J* = 15.8 and 6.3 Hz, 1H; CH), 2.40 (m, 1H; CH), 2.20 (s, 3H; CH₃), 1.95 (m, 2H; CH₂), 1.68 (m, 1H; CH), 1.10 (s, 3H; CH₃), 1.05 (s, 3H; CH₃), and 0.95 (s, 3H; CH₃); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 204.4, 178.2, 170.1, 166.6, 90.9, 67.8, 54.8, 54.3, 51.9, 46.6, 38.0, 30.7, 30.5, 28.9, 16.6, 16.4 and 9.7; ES-MS (+ve mode): [M⁺+Na] 363.0 (100), 283.5 (8), 238.9 (20); HRMS calcd for C₁₇H₂₄O₇: 340.1522, found: 341.0980 [M⁺+H].

Crystal Data for (*S,S*)-**9**: C₂₀H₃₀O₆S₂, *M*_r = 430.56, Orthorhombic space group *P*2₁2₁2₁, *a* = 6.3432(13), *b* = 16.713(3), *c* = 20.190(4) Å, *U* = 2140.4(7) Å³, *Z* = 4, μ (MoK α) = 0.282 mm⁻¹, 5375 unique data were produced from 15601 measured reflections (*R*_{int} = 0.0891), *R*₁ = 0.0535 and *wR*₂ = 0.1172.

Crystal Data for (*S,S*)-**10**: C₁₇H₂₄O₇, *M*_r = 340.36, Monoclinic space group *P*2₁, *a* = 6.175(2), *b* = 7.547(2), *c* = 19.027(4) Å, β = 98.44(3)°, *U* = 877.1(3) Å³, *Z* = 2, μ (MoK α) = 0.1 mm⁻¹, 3611 unique data were produced from 16126 measured reflections (*R*_{int} = 0.0987), *R*₁ = 0.0528 and *wR*₂ = 0.1179. CCDC-166921 ((*S,S*)-**9**) and CCDC-127009 ((*S,S*)-**10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/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).

Received: September 5, 2001
Received: November 14, 2001 [Z17853]

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A New Mononuclear Iron(III) Complex Containing a Peroxocarbonate Ligand**

Koji Hashimoto, Shigenori Nagatomo, Shuhei Fujinami, Hideki Furutachi, Seiji Ogo, Masatatsu Suzuki,* Akira Uehara, Yonezo Maeda, Yoshihito Watanabe,* and Teizo Kitagawa*

Peroxo iron(III) complexes have been proposed as key intermediates in various oxidation reactions catalyzed by mononuclear non-heme iron enzymes and their functional model complexes.^[1] Various types of synthetic mononuclear peroxo–iron(III) complexes with η^2 -peroxo,^[2,3] η^1 -hydroperoxo,^[3,4] and alkylperoxo^[5] ligands have been characterized by spectroscopic studies. However, there is no structurally characterized mononuclear peroxo iron(III) complex to date. It has been shown that the structure, electronic structure, and reactivity of the peroxo complexes can be modified by the coordination environment at an iron(III) center. For instance, a tetradentate tripod ligand, tris(2-pyridylmethyl)amine (TPA), has been shown to form a low-spin η^1 -hydroperoxo species, whereas sterically bulky TPA derivatives with 6-methyl groups give low-spin and/or high-spin alkylperoxo species.^[5d] Furthermore, interconversion between η^2 -peroxo and η^1 -hydroperoxo species has been also observed in some complexes, where a change in spin states (high spin and low spin) also occurs.^[1c,3] Most of these peroxo–iron(III) complexes have nitrogen-rich coordination environments, except for the ethylenediaminetetraacetate (EDTA) complex. Thus, it is of interest to investigate how the nature of the donor atoms and the stereochemistry of the supporting ligands influence the formation, structure, and properties of such peroxo–iron(III) complexes. Here, we report the synthesis of a novel mononuclear iron(III) complex with a bidentate peroxocarbonate ligand in a carboxylate-rich coordination environment, [Fe(qn)₂(O₂C(O)O)]Ph₄P · 1.5 CH₃OH · 0.5 (CH₃)₂NCHO (**1**; see Figure 1), derived from the reaction of a bis(μ -hydroxo)di-iron(III) complex, [Fe₂(qn)₄(OH)₂] · 2 H₂O (**2**) with H₂O₂ and CO₂, where Hqn is quinaldic acid. Compound **1** is the first

[*] Prof. M. Suzuki, K. Hashimoto, Dr. S. Fujinami, Dr. H. Furutachi, Prof. A. Uehara

Department of Chemistry, Faculty of Science
Kanazawa University, Kakuma-machi
Kanazawa 920-1192 (Japan)
Fax: (+81) 76-264-5742
E-mail: suzuki@cacheibm.s.kanazawa-u.ac.jp

Prof. Y. Watanabe, Prof. T. Kitagawa, Dr. S. Nagatomo, Dr. S. Ogo
Institute for Molecular Science
Myodaiji, Okazaki 444-8585
(Japan)

Fax: (+81) 564-54-2254
E-mail: yoshi@ims.ac.jp, teizo@ims.ac.jp

Prof. Y. Maeda
Department of Chemistry, Faculty of Science, Kyushu University
Hakozaki, Higashiku, Fukuoka 812-0053 (Japan)

[**] Financial support of this research by the Ministry of Education, Science, and Culture Grant-in-Aid for Scientific Research to M.S., Y.W., and T.K. is gratefully acknowledged.

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

example of a crystallographically characterized transition metal complex with a peroxocarbonate ligand.

Reaction of **2** with an excess of hydrogen peroxide (>10 equivalents) in the presence of 2 equivalents of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) or tetra-*n*-butylammonium acetate ($n\text{Bu}_4\text{N}(\text{OAc})$) in dimethylformamide (DMF) at -60°C , gave a deep blue solution.^[6] This solution is not thermally stable even at -60°C and decomposed to give a reddish yellow solution under air. It was found that the decomposition was much accelerated under a CO_2 atmosphere, which suggests that CO_2 plays an important role in the decomposition of the blue species. The electrospray ionization (ESI) mass spectrum of the reddish yellow reaction mixture, in the range of m/z 150 to 1200, showed a signal at m/z 476 (relative intensity (I) = 100 %) which matches well with the calculated isotopic distribution for the complex ion, $[\text{Fe}(\text{qn})_2(\text{O}_2\text{C}(\text{O})\text{O})]^-$ (see Supporting Information, Figure S1). Complex **1** is thermally unstable and decomposed to give a yellow species in DMF within 1 h at 0°C .

The complex anion of **1** has a distorted octahedral structure with a *trans*- N_2O_4 donor set composed of a bidentate peroxocarbonate and two bidentate qn ligands (Figure 1). The peroxocarbonate forms a five-membered chelate ring with the O1-Fe-O3 angle of $78.8(1)^\circ$. The O1-O2 bond length is $1.455(5)$ Å, which is comparable to those of $\text{KH}(\text{O}_2\text{C}(\text{O})\text{O}) \cdot \text{H}_2\text{O}_2$ ($1.457(2)$ Å)^[7] and a perketyl platinum complex (1.46 Å),^[8] and in the range of those of alkylperoxo transition metal complexes (1.36 – 1.52 Å).^[9] This bond length is longer

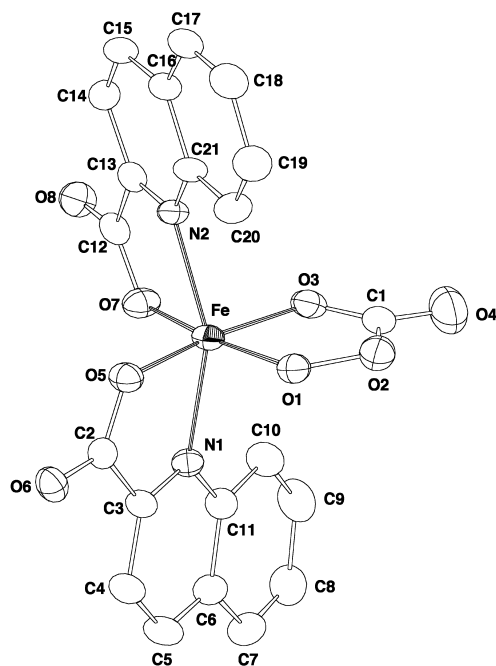


Figure 1. ORTEP view (thermal ellipsoids at 50% probability) of the anion of **1**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles $^\circ$: Fe–O1 $1.936(3)$, Fe–O3 $1.999(3)$, Fe–O5 $1.983(3)$, Fe–O7 $1.993(3)$, Fe–N1 $2.178(4)$, Fe–N2 $2.186(4)$, O1–O2 $1.455(5)$, C1–O2 $1.378(7)$, C1–O3 $1.282(6)$, C1–O4 $1.236(7)$; O1–Fe–O3 $78.8(1)$, O1–Fe–O5 $88.3(1)$, O1–Fe–O7 $166.9(1)$, O1–Fe–N1 $93.6(1)$, O1–Fe–N2 $106.0(1)$, O3–Fe–O5 $167.1(1)$, O3–Fe–O7 $88.4(1)$, O3–Fe–N1 $103.0(1)$, O3–Fe–N2 $94.9(1)$, O5–Fe–O7 $104.5(1)$, O5–Fe–N1 $78.1(1)$, O5–Fe–N2 $88.2(1)$, O7–Fe–N1 $86.4(1)$, O7–Fe–N2 $77.8(1)$, N1–Fe–N2 $155.8(1)$, Fe–O1–O2 $115.0(2)$, O1–O2–C1 $112.2(4)$.

than the corresponding lengths in *cis*- μ -1,2-peroxo diiron(III) complexes ($1.406(8)$ – $1.426(6)$ Å)^[10] and comparable to those of μ_4 -peroxo hexa-iron(III) complexes (1.47 – 1.48 Å).^[11] The Fe–O1 bond length ($1.936(3)$ Å) is intermediate between the average Fe–O bond length of the *cis*- μ -1,2-peroxo diiron(III) complexes (1.89 Å) and μ_4 -peroxo hexa-iron(III) complexes (2.04 Å). The Fe–O1–O2 angle ($115.0(2)^\circ$) in **1** is comparable to those of μ_4 -peroxo hexa-iron(III) complexes (113 – 116°) and smaller than those of *cis*- μ -1,2-peroxo diiron(III) complexes (118.1 – 129.5°). The C–O bond lengths (C1–O2, C1–O3, and C1–O4) of the peroxocarbonate ligand are $1.378(7)$, $1.282(6)$, and $1.236(7)$ Å, respectively, which are also similar to those of $\text{KH}(\text{O}_2\text{C}(\text{O})\text{O}) \cdot \text{H}_2\text{O}_2$ ($1.381(2)$, $1.249(2)$, and $1.229(2)$ Å).^[7] The short C1–O4 bond length suggests double bond character.

The electron paramagnetic resonance (EPR) spectrum of a frozen DMF–ethanol solution of **1** at 78 K showed a signal at $g = 4.3$, arising from a high-spin iron(III) center (see Supporting Information, Figure S2). The electronic spectrum of **1** in DMF at -60°C (Figure 2) shows an intense absorption band

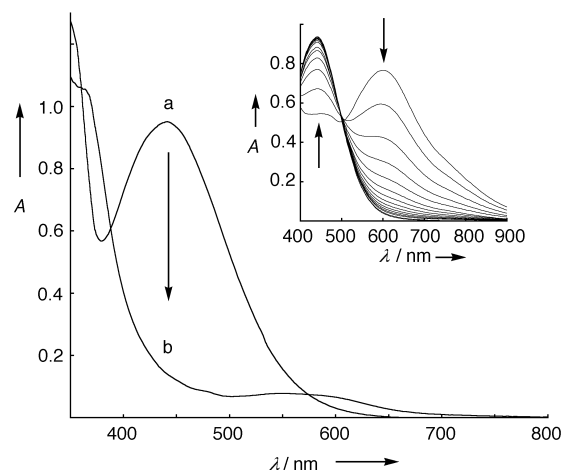


Figure 2. Electronic spectra of **1** (a) in DMF ($[\text{Fe}] = 0.64$ mM) at -60°C and its decomposed species (b) at room temperature. Inset: spectral change for the formation of **1** by flowing CO_2 over the deep blue solution, generated by the reaction of **2** in DMF ($[\text{Fe}] = 0.33$ mM) with 10 equivalents of H_2O_2 , in the presence of 2 equivalents of DBU, at -60°C . The spectra were measured by an optical-fiber apparatus with a corrected light path length of 1.03 cm.

at 440 nm ($\epsilon = 1450 \text{ M}^{-1} \text{ cm}^{-1}$), which may be assigned to the ligand to metal charge transfer (LMCT) transition from the peroxocarbonate ligand (π_v^* orbital of the peroxo moiety) to the iron(III) center ($d\pi$ orbital). The corresponding LMCT transitions of the mononuclear hydroperoxo^[3, 4] and alkylperoxo^[5] iron(III) complexes, irrespective of their spin state (low spin or high spin), have been observed at 506 – 640 nm. Thus, the LMCT transition energy of **1** is substantially blue-shifted relative to those of the other complexes. For fuller understanding of such a significant blue-shift of the LMCT transition, further study is needed.

The resonance Raman spectrum of **1**, measured in DMF at approximately -60°C with a 514.5 nm laser excitation, showed five isotope sensitive bands at 965 , 884 , 728 , 578 , and 547 cm^{-1} , which were shifted to 946 ($\Delta\nu = -19$), 841

($\Delta\nu = -43$), 710 ($\Delta\nu = -18$), 564 ($\Delta\nu = -14$), and 524 cm^{-1} ($\Delta\nu = -23$) by use of ^{18}O (Compare Figure 3 a and b).^[12] The band at 965 cm^{-1} is also isotope sensitive; a sample prepared by use of $^{13}\text{CO}_2$ showed a band at 960 cm^{-1} ($\Delta\nu = -5$; Figure 3 c), which indicates that CO_2 is the carbon source of the peroxocarbonate ligand. No significant shifts were ob-

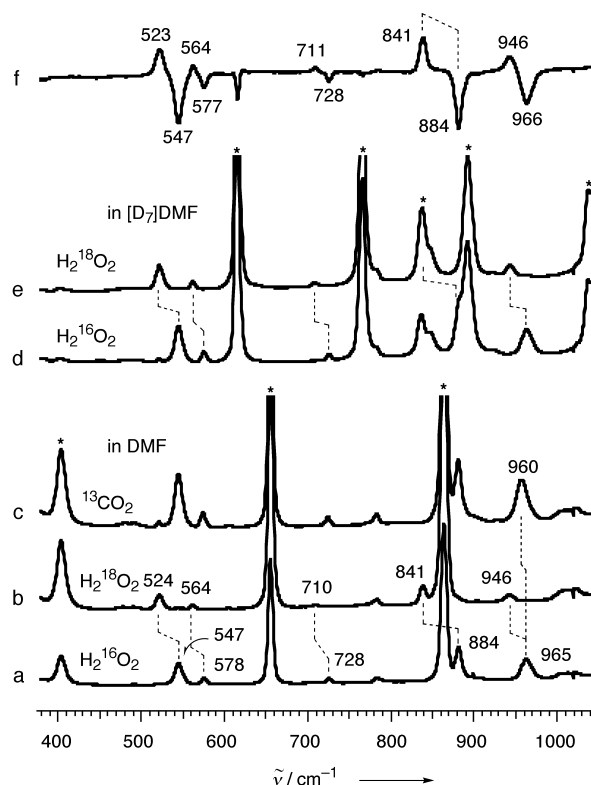


Figure 3. Resonance Raman spectra of **1** produced from $\text{H}_2^{16}\text{O}_2$ (a), $\text{H}_2^{18}\text{O}_2$ (b), $^{13}\text{CO}_2$ (c) in DMF at approximately -60°C . Resonance Raman spectra of **1** produced in $[\text{D}_7]\text{DMF}$ at approximately -60°C from $\text{H}_2^{16}\text{O}_2$ (d) and $\text{H}_2^{18}\text{O}_2$ (e), and the difference spectrum (f) of the spectra (d) and (e) with 514.5 nm excitation. *: solvent bands.

served for the other bands ($0-2\text{ cm}^{-1}$). The band at 884 cm^{-1} is assigned to the $\tilde{\nu}(\text{O}-\text{O})$ stretching vibration, as the magnitude of shift to lower wavenumber by ^{18}O substitution is -43 cm^{-1} (-50 cm^{-1} for diatomic harmonic oscillators), which compares well with those of the peroxo complexes. Unlike **1**, the Raman spectra of the alkylperoxo iron(III) complexes in a high-spin state exhibit two bands at around 880 cm^{-1} and 840 cm^{-1} , attributed to a significant mixing of the $\nu(\text{O}-\text{O})$ and $\nu(\text{C}-\text{O})$ vibrations of the alkylperoxo groups. It is noted that the infrared spectra of $[\text{RhCl}(\text{O}_2\text{C}(\text{O})\text{O})(\text{PET}_2\text{Ph})_3]$ (**3**) showed the $\nu(\text{O}-\text{O})$ band at 963 cm^{-1} ($\Delta\nu = -20\text{ cm}^{-1}$) reported by Aresta et al.,^[13] which is shifted to a significantly higher wavenumber than that of **1**. The isotope labeling experiments of **3** revealed that the formation of the peroxocarbonate ($^{18}\text{O}-^{16}\text{O}-\text{C}(^{16}\text{O})^{18}\text{O}$) proceeds through $^{18}\text{O}-^{18}\text{O}$ bond cleavage of the η^2 -peroxo ligand and C^{16}O_2 insertion. Unlike **3**, the formation of the peroxocarbonate unit in **1** appears to proceed by a nucleophilic addition of a peroxo group to CO_2 without the $\text{O}-\text{O}$ bond cleavage, because the isotope labeling experiments showed a large $\Delta\nu$ value (-43 cm^{-1}), and there is no

$\nu(^{16}\text{O}-^{18}\text{O})$ band between 884 cm^{-1} ($\nu(^{16}\text{O}-^{16}\text{O})$) and 841 cm^{-1} ($\nu(^{18}\text{O}-^{18}\text{O})$); see Figure 3 d, e, and f). The band of **1** at 965 cm^{-1} , which is isotope sensitive for both ^{13}C ($^{13}\text{CO}_2$) and ^{18}O ($\text{H}_2^{18}\text{O}_2$) substitutions, is attributed to the $\text{O}-\text{O}-\text{C}(\text{O})\text{O}$ moiety. It is also notable that there are two isotope-sensitive bands at 578 and 547 cm^{-1} in the $\nu(\text{Fe}-\text{O})$ stretching-vibration region.

In summary, we have succeeded for the first time in the structural characterization of a novel peroxocarbonate iron(III) complex (**1**) produced by the nucleophilic addition of a peroxide to CO_2 . The peroxocarbonate ligand forms a five-membered chelate ring, which is responsible for the stabilization of the peroxocarbonate ligand. Compound **1** has an oxidation activity toward triphenylphosphane to triphenylphosphane oxide, but not toward olefins such as cyclohexene.

Experimental Section

1: A suspension of **2** (435 mg, 0.5 mmol) in DMF (30 mL) was dissolved by addition of DBU or $n\text{Bu}_4\text{N}(\text{OAc})$ (2 equivalents), and the resulting yellow solution was cooled to -60°C . H_2O_2 (10 equivalents) was added to give a blue solution. A stream of CO_2 gas was passed over the blue solution at -60°C for 30 min to afford a reddish yellow solution, to which Ph_4PBr (419 mg, 1 mmol) in methanol (30 mL) was added. The resulting solution was allowed to stand at -60°C for a week to give orange crystals suitable for X-ray crystallography. Compound **1** was also prepared in a similar manner using acetonitrile as the solvent instead of DMF.

ESI mass spectra were obtained with an API 300 triple quadrupole mass spectrometer (PE-Sciex) in negative ion detection mode, equipped with an ion spray interface. A DMF solution produced by the reaction of **2** with H_2O_2 , in the presence of DBU and CO_2 at -60°C , was diluted with MeCN (1:19) and the resulting solution was introduced to the ionization source through a capillary, by the use of high Ar pressure at -40°C .

Crystal data for **1**: triclinic, $P\bar{1}$, $a = 11.8188(5)$, $b = 13.866(2)$, $c = 13.7010(9)\text{ \AA}$, $\alpha = 83.806(3)$, $\beta = 86.610(4)$, $\gamma = 87.059(2)^\circ$, $V = 2226.0(3)\text{ \AA}^3$, $\rho_{\text{calc}} = 1.343\text{ g cm}^{-3}$, $Z = 2$, $0.35 \times 0.20 \times 0.05$, $T = -160^\circ\text{C}$, $F_{000} = 936.00$, $\mu(\text{MoK}\alpha) = 4.36\text{ cm}^{-1}$, Rigaku Mercury CCD diffractometer, $\text{MoK}\alpha$ ($\lambda = 0.71070\text{ \AA}$), ω scans, 9240 measured, 6478 independent reflections ($I > 3.00\sigma(I)$), 556 parameters; structure solution with direct methods^[14] and successive Fourier technique.^[15] All non-hydrogen atoms of the complex anion and the counter ion, except for the disordered ones, were refined with anisotropic displacement parameters. Hydrogen atoms were placed at calculated positions ($0.95\text{ \AA}$). They were included, but not refined against $|F|$, to yield R (R_w) = 0.079 (0.116); largest residual electron densities 1.08/−0.81 near the iron atom (GOF = 2.03). CCDC-172141 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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).

Received: October 17, 2001 [Z18074]

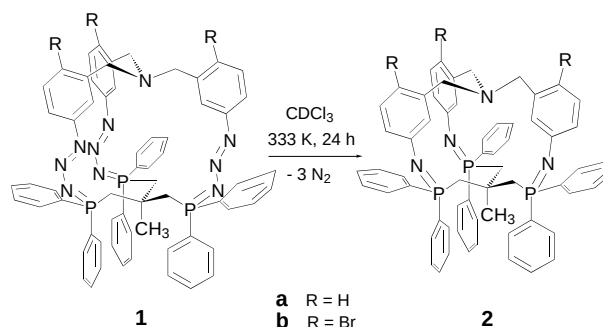
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Helical Sense Bias Induced by Point Chirality in Cage Compounds**

Mateo Alajarín,* Carmen López-Leonardo, Angel Vidal, José Berná, and Jonathan W. Steed*

Dedicated to Professor José Elguero

At the molecular level, helical chirality^[1] is usually a consequence of strong conformational preferences around covalent bonds. This is the case in molecular propellers, chiral molecules possessing two or more subunits which can be considered as “blades” (e.g., aryl or spirocyclic rings), which radiate from an axis of rotation (propeller axis).^[2] Triaryl-methanes are the most extensively studied structures of this class.^[3] Bicyclic organic compounds of local C_3 symmetry, constructed by linking two propeller tripodal units exhibit this type of chirality. However, this propeller shape has been observed only for a limited number of such compounds in solution.^[4] We have reported the preparation of several types of C_3 or pseudo- C_3 symmetric, chiral macrobicyclic triphosphazides (e.g. **1a**, Scheme 1), which possess propeller-like topology in solution and in the solid state.^[5]



Scheme 1. Synthesis of **2** by dinitrogen expulsion from **1**.

Herein, we report that, when compound **1a** was kept at 333 K in $CDCl_3$ solution for 24 h, it cleanly converted into tri- λ^5 -phosphazene **2a** in 75 % yield, by triple expulsion of molecular N_2 (Scheme 1). The dinitrogen expulsion from

[*] Dr. M. Alajarín, Dr. C. López-Leonardo, Dr. A. Vidal, J. Berná
Departamento de Química Orgánica
Facultad de Química, Campus de Espinardo
Universidad de Murcia, 30100 Murcia (Spain)
Fax: (+349) 68-364149
E-mail: alajarin@um.es
Dr. J. W. Steed
Department of Chemistry
King's College London
Strand, London WC2R 2LS (UK)
Fax: (+44) 20-7848 2810
E-mail: jon.steed@kcl.ac.uk

[**] We thank the Dirección General de Investigación-MCYT (Project BQU2001-0010), Fundación Séneca-CARM (Projects PB/2/FS/01 and PI-1/00749/FS/01), and Acedesa (a division of Takasago) for financial support. J.B. also thanks the MECO for a fellowship. J.W.S. thanks the EPSRC and King's College London for diffractometer funding.

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

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each PN_3 unit can be understood as the second mechanistic step of a Staudinger P^{III} imination reaction.^[6]

The new cage compound **2a** was fully characterized by its analytical and spectroscopic data,^[7] but we were unable to obtain a crystalline sample suitable for molecular structure determination by X-ray crystallography. To overcome this problem we prepared the new triphosphazide **1b**, by our well-established methodology,^[5b,c] which was then heated in solution (CDCl_3) to yield the tri- λ^5 -phosphazene **2b** (74%). Suitable crystals of **2b** enabled analysis of the molecular structure.^[8] Two perspective views of the structure of **2b** are shown in Figure 1. The molecule is located on a non-crystallographic threefold axis passing through the two bridgehead atoms of the bicyclic cage, and its propeller-

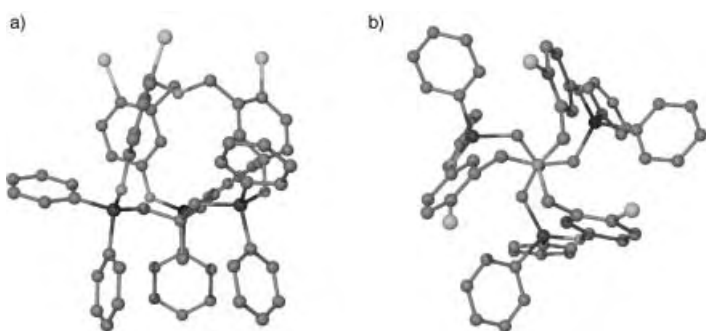


Figure 1. a) Molecular structure of **2b** (hydrogen atoms omitted for clarity), b) perspective view as projected along the threefold axis.

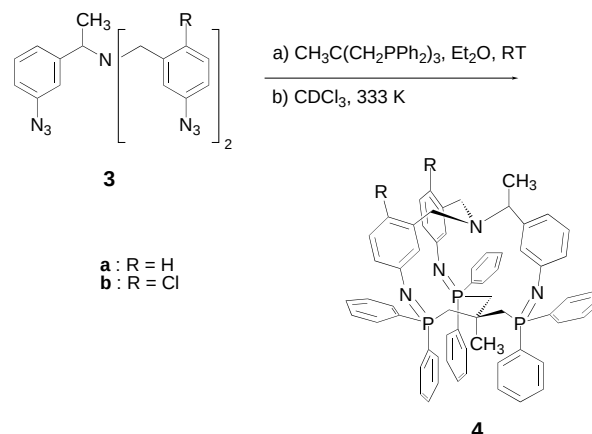
like shape is clearly apparent when the molecule is viewed along this axis (Figure 1b). Both propeller units, the upper tribenzylamine core and the lower *tert*-pentane fragment, present the same helical twist sense, $M^{[9]}$ (Figure 1b). The twist apparently arises from the need to minimize the volume of the unoccupied molecular cavity. The cavity is too small to include any available guest species and therefore screws down upon itself like the lid of a screw-top jar, which results in a cavity of almost negligible volume. Four molecules of chloroform cocrystallize with **2b**. One of these chloroform molecules engages in a $\text{CH}\cdots\text{N}$ hydrogen bond to one of the $\text{N}=\text{P}$ nitrogen atoms ($\text{C}\cdots\text{N}$ 3.155 Å), while the others form strong $\text{CH}\cdots\pi$ -system interactions with $\text{H}\cdots$ centroid distances both approximately 2.45 Å ($\text{C}\cdots$ centroid 3.388 and 3.413 Å).

The NMR spectroscopic data of compound **2b** in CDCl_3 solution at 298 K (particularly the magnetic nonequivalence of the diastereotopic ligands), similar to those of **2a**, revealed that the solid state conformation of compounds **2** is probably retained in solution at 298 K. High-temperature ^1H NMR experiments (compound **2b**, $o\text{-Cl}_2\text{C}_6\text{D}_4$ solution) demonstrated the simultaneous coalescence of the signals of the methylene CH_2N and CH_2P protons at 423 K. At this temperature, the coalescence of signals for the two phenyl groups on the phosphorus atom was also observed in the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum. On cooling to 298 K, the spectrum recovered its original appearance. These results are explained by equilibration, at the coalescence temperature, between the two enantiomeric propeller-like forms of **2b** via a labile confor-

mation with time-averaged C_{3v} symmetry. The calculated^[10] activation energy of this racemization process, $\Delta G^\ddagger = 20.8 \text{ kcal mol}^{-1}$, is notably higher than the values found in other bicyclic molecular propellers^[4b,d] and slightly higher than those of some tricyclic [4.4.4]propellanes^[11] and the 1-azonia[4.4.4]propellane cation.^[12] When a similar high-temperature NMR spectroscopy experiment was carried out with **2b** in wet $[\text{D}_6]\text{DMSO}$ solution, the results were comparable to those above, but surprisingly no trace of hydrolysis of the tri- λ^5 -phosphazene was observed, which reveals the chemical stability of compounds **2** to be in sharp contrast with the hydrolytic sensitivity of most of the λ^5 phosphazenes prepared to date.^[13]

To our knowledge, compounds **2** are the first examples of bicyclic tri- λ^5 -phosphazenes, a subclass of the rare species bearing intracyclic phosphazene units,^[14] and the conversion of **1** into **2** is the first observation of nitrogen expulsion from a fully characterized cyclic phosphazide.^[15]

We then wondered if the sense of twist (*P/M*) of the helical asymmetry of cages type **2** could be controlled by the configuration of a single chiral carbon atom on one of the arms. By using standard methods, we synthesized α -methyl substituted triazides **3** in racemic form, which were converted into tri- λ^5 -phosphazenes **4** (Scheme 2).



Scheme 2. Preparation of α -methyl tri- λ^5 -phosphazenes **4**.

Although two diastereomeric pairs (*R,P/S,M* and *R,M/S,P*) are possible for both **4a** and **4b**, these compounds were obtained as single diastereoisomers in 70 and 63 % yield, respectively (based on the starting triazides). An X-ray crystal structure determination showed **4b** to be the *R,M/S,P* diastereoisomer (Figure 2). The same stereochemistry was assumed for **4a** as a consequence of the close similarity of its spectral data to that of **4b**.

These results demonstrate that the helical asymmetry of the bicyclic, propeller-like cages **4** is totally controlled by the absolute configuration of their single stereogenic benzylic carbon atoms. This control seems to be determined by the marked preference of the methyl group for the occupation of a 'pseudoaxial' position (parallel to the pseudo C_3 axis)

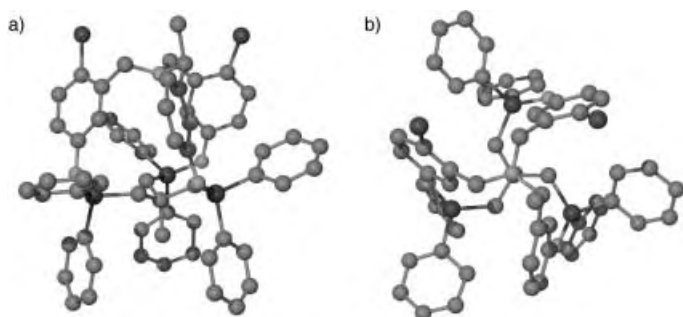
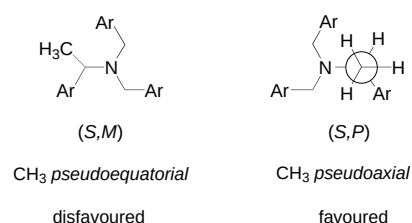


Figure 2. Molecular structure of **4b** with hydrogen atoms omitted for clarity a) side view, b) perspective view as projected along the *pseudo*-threefold axis.

instead of the alternative pseudoequatorial situation closer to the internal cavity, and therefore to the aryl groups. The sense of twist of the arm bearing the α -methyl group in turn determines those of the other two arms (Scheme 3).^[16]



Scheme 3.

The calculated^[17] difference in energy between both diastereoisomers of **4b** is 3.89 kcal mol⁻¹ in favor of the one present in the crystal. When enantioenriched (–)-(*S*)-**3b** (98% *ee*) was used in the procedure described in Scheme 2, optically active (*S,P*)-**4b** ($\alpha_D = +398.4^\circ$, $c = 6.20 \times 10^{-3}$ in CHCl₃) of definite helical sense was obtained.

The present case of point-to-helix chirality transfer at the molecular level in discrete organic compounds may be added to the limited number of such cases reported mainly in metal-coordinated systems^[18] and polymeric superstructures.^[19]

Experimental Section

General synthesis of 2: A solution of compound **1** (5 mL, 1 mmol, 0.2 M in CDCl₃) placed in a loosely sealed round-bottom flask, immersed in an oil bath, was heated at 60 °C for 24 h. After cooling, the solvent was removed under reduced pressure and the crude product was crystallized from a mixture of dichloromethane and diethyl ether. In this way compounds **2a** and **2b** were obtained in 75% and 74% yield, respectively.

General synthesis of *rac*-tribenzylamines 3: The corresponding 3-azidobenzyl iodide (4 mmol) was added to a solution of *rac*-1-(3-azidophenyl)ethylamine (30 mL, 2 mmol, 0.07 M in dioxane). The mixture was heated under reflux stirring for 4 h. After cooling to room temperature, an excess of triethylamine (0.45 g, 4.5 mmol) was added at once, and the mixture stirred for 2 h. The precipitated triethylammonium iodide was separated by filtration. The dioxane was removed from the filtrate under reduced pressure and the residue was chromatographed (silica gel; ethyl acetate/*n*-hexane (1:9)). In this way compounds **3a** and **3b** were obtained in 44% and 27% yield, respectively.

Preparation of (*S*)-3b**:** *rac*-1-(3-Azidophenyl)ethylamine (1.84 g, 11.3 mmol) and (*R,R*)-tartaric acid (1.70 g, 11.3 mmol) were dissolved in hot methanol (40 mL). The solution was cooled to room temperature. After 12 h, the supernatant liquid was separated and the white solid was

recrystallized from hot methanol (25 mL). After 16 h at room temperature, the solid was collected by filtration and dried to give the amine–tartrate salt (0.84 g). The salt was suspended in dichloromethane (30 mL), 1 M NaOH (20 mL) was added and the mixture was stirred for 1 h. The organic layer was separated, the aqueous layer was extracted twice (CH₂Cl₂, 2 × 20 mL), and the combined organic extracts were dried over MgSO₄. The solvent was removed under reduced pressure to give (*S*)-1-(3-azidophenyl)ethylamine (0.41 g, 45%). The α -methoxy- α -phenyl- α -(trifluoromethyl)acetamide of this material was prepared from (*R*)-(+)- α -methoxy- α -trifluoromethylbenzeneacetic acid (MPTA) and *N,N'*-dicyclohexylcarbodiimide (DCC) and analyzed by ¹H and ¹⁹F NMR spectroscopy to reveal a diastereoisomeric ratio of 95:5, the major isomer was the (*S*)-1-(3-azidophenyl)ethylamine. A third recrystallization of the amine–tartrate salt from methanol (15 mL) afforded 0.63 g of the salt, which yielded (*S*)-1-(3-azidophenyl)ethylamine upon addition of base $\alpha_D^{20} = -26.2^\circ$ ($c = 8.3 \times 10^{-3}$ in CHCl₃, 98% *ee*). Mosher amide of (*S*)-1-(3-azidophenyl)ethylamine: yield 94%; m.p. 69–71 °C; ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): $\delta = 1.49$ (d, $J = 6.8$ Hz, 3H, CH₃), 3.43 (d, $J = 6.8$ Hz, 3H, OCH₃), 5.14 (q, $J = 6.8$ Hz, 1H, CH), 7.12 (m, 9H); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 21.53$ (CH₃), 48.65 (OCH₃), 54.94 (CH), 84.15 (q, $J(C,F) = 26.7$ Hz, CCF₃), 116.66, 118.08, 122.72, 123.75 (q, $J(C,F) = 289.5$ Hz, CF₃), 127.56, 128.19, 128.51, 129.00, 129.50, 130.04, 132.37 (q), 140.42 (q), 144.70 (q), 165.46 (q, CO); ¹⁹F NMR (282.4 MHz, CDCl₃, 25 °C): $\delta = 9.07$; IR (Nujol): $\tilde{\nu} = 2121$ (N₃), 1690 (C=O) cm⁻¹. The alkylation of (*S*)-1-(3-azidophenyl)ethylamine with 3-azido-6-chlorobenzyl iodide as above yielded (*S*)-**3b** in 22% yield. $\alpha_D^{20} = -33.0^\circ$ ($c = 6.0 \times 10^{-3}$ in CHCl₃).

General synthesis of 4: Two solutions of the corresponding tribenzylamine **3** (5 mL, 0.5 mmol, 0.1 M in CDCl₃) and [2-((diphenylphosphino)methyl)-2-methyl-1,3-propanediyl]bis[diphenylphosphine] (TRIPHOS; 5 mL, 0.5 mmol, 0.1 M in CDCl₃) were simultaneously added to a round-bottom flask containing CDCl₃ (10 mL) under nitrogen at room temperature, over a period of 1 h with stirring. The resulting mixture was then stirred for about 3 h (monitoring by IR) at room temperature. After this time, the mixture was placed in an oil bath and heated at 60 °C for 24 h. After cooling, the solvent was removed under reduced pressure and the crude product was crystallized from a mixture of chloroform and hexane. The compounds **4a** and **4b** were obtained in 70% and 64% yield, respectively.

Received: November 9, 2001 [Z18193]

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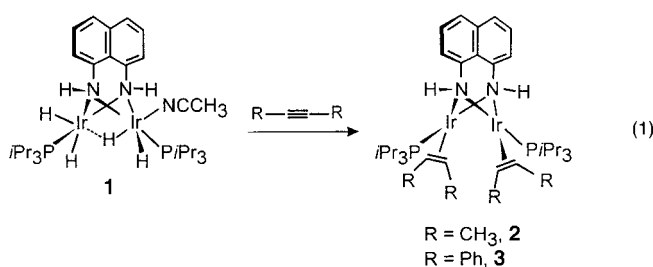
Alkene C–H Activations at Dinuclear Complexes Promoted by Oxidation**

M. Victoria Jiménez, Eduardo Sola, Javier Caballero, Fernando J. Lahoz, and Luis A. Oro*

Several recent discoveries in the chemistry of transition metal di- and polynuclear complexes have disclosed new methods of hydrocarbon activation and functionalization, favored by polynuclear environments.^[1, 2] In parallel, considerable progress has been made in understanding the reactivity features resulting from multimetallic reaction sites.^[1, 3, 4] Together, such advances may contribute to the rational design of new catalysts and applications based on this type of compound. However, the proximity of the metal centers is likely to have significant repercussions for the reactivity, which remain to be determined.

In our recent studies on “open-book” d⁸ diiridium complexes with N-donor bridges, we have observed a remarkable substrate selectivity in the reactions of these compounds towards oxidative addition reactants. Whereas the d⁸ diiridium complexes underwent fast S_N2 oxidative additions with substrates such as halocarbons,^[4] the additions of less-polar reactants such as dihydrogen were not observed. The oxidation of these d⁸d⁸ diiridium compounds, to species of d⁶d⁸ or d⁷d⁷ electronic configurations, gave dihydrogen-activating compounds.^[5] Here we report that such an oxidation strategy also allows the transformation of nonreactive d⁸d⁸ compounds into dinuclear C–H activating species.

The treatment of the diamidonaphthalene ((NH₂)naphth)-bridged diiridium(III) complex [Ir₂(μ-1,8-(NH)₂naphth)-(μ-H)H₃(NCCH₃)(PiPr₃)₂] (**1**) with two equivalents of an internal alkyne such as 2-butyne or diphenylacetylene afforded diiridium(I) derivatives of the formula [Ir₂(μ-1,8-(NH)₂naphth)(η²-Z-RHC=CHR)₂(PiPr₃)₂] (R = Me (**2**), Ph (**3**)) [Eq. (1)]. The solution NMR spectra of both compounds indicate symmetric C₂ structures with a transoid arrangement of nonrotating Z-alkene ligands. These features have been confirmed by the X-ray crystallographic determination of the structure of **2**,^[6] (Figure 1).



[*] Prof. Dr. L. A. Oro, Dr. M. V. Jiménez, Dr. E. Sola, Dipl.-Chem. J. Caballero, Dr. F. J. Lahoz
Departamento de Química Inorgánica
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza-CSIC
50009 Zaragoza (Spain)
Fax: (+34) 976-761143
E-mail: oro@posta.unizar.es

[**] We are grateful to the Plan Nacional de Investigación, Ministerio de Ciencia y Tecnología, for the support of this research (Project No. BQU2000-1170).

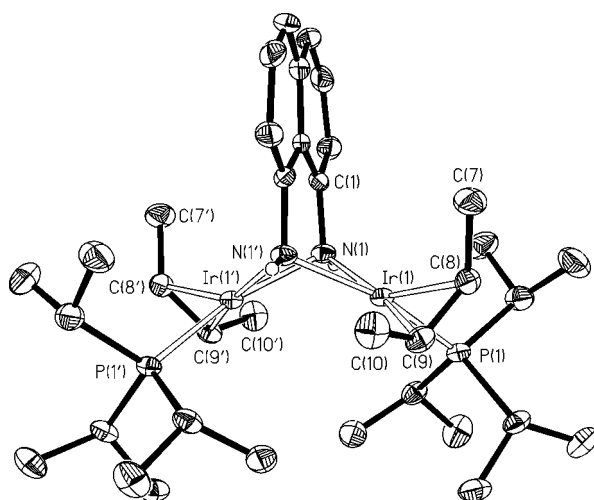


Figure 1. Molecular representation of the dinuclear complex **2**. Atoms labeled with a prime are related to the corresponding unprimed ones by the symmetry transformation $1 - x, y, -z + 3/2$. Selected interatomic distances [Å] and angles [°]: Ir(1)⋯Ir(1') 2.9863(3), Ir(1)–P(1) 2.2336(10), Ir(1)–N(1) 2.124(3), Ir(1)–N(1') 2.125(3), Ir(1)–C(8) 2.111(4), Ir(1)–C(9) 2.158(4), C(8)–C(9) 1.414(6); P(1)–Ir(1)–N(1) 97.32(10), P(1)–Ir(1)–N(1') 164.34(9), N(1)–Ir(1)–N(1') 72.62(16), N(1')–Ir(1)–C(9) 91.28(15), C(7)–C(8)–C(9) 123.3(4), C(8)–C(9)–C(10) 121.5(4).

The alkene ligands of compounds **2** and **3** were found to be relatively nonlabile, they remained coordinated after the treatment of **2** and **3** with an excess of ligands such as pyridine, ethylene, or alkynes, but were slowly replaced by CO to give the known complex $[\text{Ir}_2(\mu\text{-}1,8\text{-(NH)}_2\text{naphth})(\text{CO})_2(\text{P}i\text{Pr}_3)_2]$.^[5] The oxidation of **2** and **3** by $[\text{FeCp}_2](\text{CF}_3\text{SO}_3)$ took place under conditions similar to those employed for the oxidation of related diiridium(II) derivatives to metal–metal bonded diiridium(III) species.^[5] Instead of the expected diiridium(III) oxidation products, the reactions afforded the hydride-bridged diiridium(III) complexes **4** and **5** [Eq. (2)], after the oxidative addition of an alkene ligand C–H bond.

As indicated by the structures deduced for **4** and **5**, the selectivity of the C–H activation step is dependent on the nature of the alkene ligand. Whereas the *Z*-stilbene ligand of **3** was activated to give an alkenyl group, the *Z*-2-butene moiety of complex **2** underwent an allylic activation to afford a more stable η^3 -allyl ligand.^[7] The reaction sequence which leads to **4** and **5** also influences the nonactivated alkene

ligands, which were labilized and substituted by acetonitrile solvent molecules.

Figure 2 shows the X-ray structure of complex **4**,^[8] in which the bridging hydride atom is nonequidistant from the metal atoms. Such an asymmetric position, which is most likely the result of the different *trans* influences exerted by the ligands

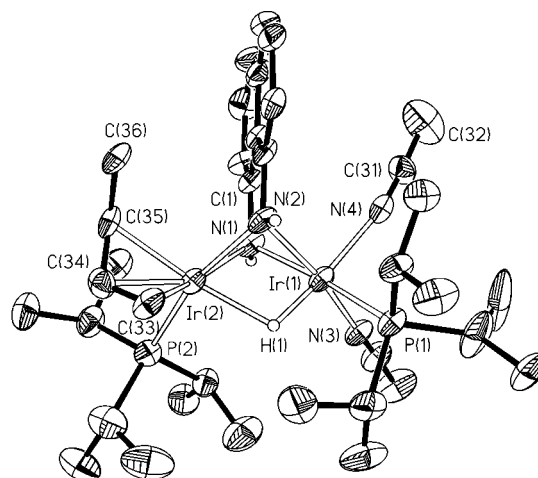
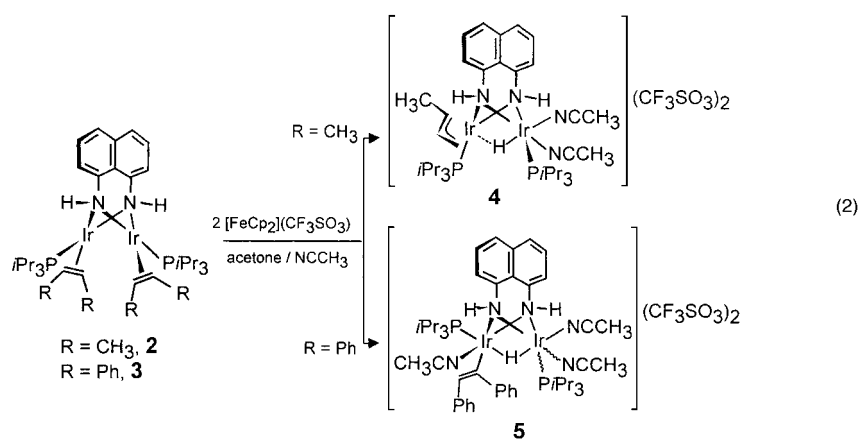


Figure 2. Molecular representation of the dicationic complex **4**. Selected interatomic distances [Å] and angles [°]: Ir(1)⋯Ir(2) 2.6938(4), Ir(1)–P(1) 2.3297(19), Ir(1)–N(1) 2.136(6), Ir(1)–N(2) 2.066(6), Ir(1)–N(3) 2.020(6), Ir(1)–N(4) 2.064(7), Ir(1)–H(1) 1.48(7), Ir(2)–H(1) 1.93(7), Ir(2)–P(2) 2.327(2), Ir(2)–N(1) 2.090(7), Ir(2)–N(2) 2.130(6), Ir(2)–C(33) 2.170(8), Ir(2)–C(34) 2.122(9), Ir(2)–C(35) 2.157(7), C(33)–C(34) 1.380(13), C(34)–C(35) 1.421(12); P(1)–Ir(1)–N(1) 170.82(19), N(2)–Ir(1)–N(3) 167.0(2), N(4)–Ir(1)–H(1) 174(3), P(2)–Ir(2)–N(2) 163.23(16), N(1)–Ir(2)–C(33) 161.1(3), C(35)–Ir(2)–H(1) 158(2), C(33)–C(34)–C(35) 119.6(9), C(34)–C(35)–C(36) 122.3(9).

trans to this bridge,^[3c, 9] is also inferred from the solution ^1H NMR signal of the hydride atom: a doublet of doublets at $\delta = -20.14$ with $J(\text{H}, \text{P})$ coupling constants of 7.8 and 3.3 Hz. A similar pattern is found for the bridging-hydride ^1H NMR signal of the starting complex **1**, which also suggests an asymmetric position for this bridge. The hydride ligand of **5** displays a ^1H NMR signal in CD_2Cl_2 , which consists of a doublet of doublets at $\delta = -17.86$ with $J(\text{H}, \text{P})$ coupling constants of 49.5 and 11.1 Hz. The large value of the former coupling constant indicates a bridging hydride *trans* to one $\text{P}i\text{Pr}_3$ ligand,^[5] which supports the proposed structure depicted in Equation (2). This proposal is also consistent with the presence in the ^1H NMR spectrum of a singlet at $\delta = 6.86$, which corresponds to the vinylic hydrogen, and three singlets at $\delta = 1.03$, 2.55, and 2.90, attributed to three nonequivalent acetonitrile ligands.

The reactivity described above indicates that the C–H oxidative addition capability of these d^8 dinuclear complexes is enhanced upon oxidation. This behavior, which apparently contradicts well-established ideas about oxidative addition to metal complexes, can be rationalized if the molecular orbital features typical of these compounds



are considered. It has been shown that the bending of these dinuclear molecules towards the open-book structure is caused by attractive metal...metal interactions, which result from donor-acceptor interactions between the full d_z and the empty p_z orbitals of the two d^8 metal atoms.^[10] The involvement of the p_z orbitals in such weak interactions could reduce their availability for other purposes, such as the C-H bond pre-coordination required for an oxidative addition,^[11] thus accounting for the inertness of these d^8 compounds towards C-H bonds. A likely consequence of the partial oxidation of the d^8d^8 core is the modification of such an unfavorable orbital situation to give more accessible empty orbitals and consequently an enhanced C-H activation capability.

The chemistry herein illustrates the profound effect that weak intermetallic interactions exert upon the reactivity of dinuclear compounds. The inertness induced by such weak interactions in open-book d^8 dinuclear compounds appears to cause the promotion of C-H oxidative additions by oxidation, a result hardly predictable from the chemistry of mononuclear complexes.

Experimental Section

All compounds gave correct elemental analyses. In the spectroscopic data lists, the signals corresponding to the $\text{P}(\text{Pr})_3$ and to the naphthalene protons and carbons have been omitted.

1: The compound was prepared as a white solid (62% yield) following the procedure described in [9] for its bispyrazolate-bridged analogue. ^1H NMR (300 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = -23.15$ (dd, $J(\text{H,P}) = 21.3$ Hz, $J(\text{H,H}) = 8.7$ Hz, 1H, Ir-H), -22.18 (ddd, $J(\text{H,P}) = 24.9$, 2.1 Hz, $J(\text{H,H}) = 8.7$ Hz, 1H, Ir-H), -20.36 (dd, $J(\text{H,P}) = 20.4$ Hz, $J(\text{H,H}) = 3.6$, 1H, Ir-H), -19.93 (ddd, 1H, $J(\text{H,P}) = 12.9$, 2.1 Hz, $J(\text{H,H}) = 3.6$ Hz, Ir-H), 0.20 (s, NCCH_3 , 3H), 4.22 (br, 2H, NH); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 29.72$ (s), 39.12 (s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = -0.18$ (s, NCCH_3), 114.36 (s, NCCH_3); MS (FAB⁺, benzene): m/z [%]: 864 (100) [$M^+ - \text{NCCH}_3$].

2 and 3: A solution of **1** (200 mg, 0.22 mmol) in toluene (10 mL) was treated with the alkyne (0.45 mmol) and stirred for 8 h at 293 K (**2**) or at 323 K (**3**). The red solid, formed after the concentration of the solution to about 2 mL, was separated from the liquid by decantation, washed with methanol and dried in vacuo. **2:** Yield: 180 mg, 84%; ^1H NMR (300 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 0.95$ (d, $J(\text{H,H}) = 6.2$ Hz, 6H, CHCH_3), 1.09 (d, $J(\text{H,H}) = 6.9$ Hz, 6H, CHCH_3), 2.06 (q, $J(\text{H,H}) = 6.2$ Hz, 2H, CHCH_3), 3.16 (q, $J(\text{H,H}) = 6.9$ Hz, 2H, CHCH_3), 5.28 (br, 2H, NH); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 13.83$ (s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 11.52$ (s, CHCH_3), 14.54 (s, CHCH_3), 23.73 (s, CHCH_3), 42.78 (s, CHCH_3). **3:** Yield: 226 mg, 82%; ^1H NMR (300 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 3.33$ (d, $J(\text{H,H}) = 9.3$ Hz, 2H, CHPh), 4.71 (dd, $J(\text{H,P}) = 9.6$ Hz, $J(\text{H,H}) = 9.3$ Hz, 2H, CHPh), 5.10 (br, 2H, NH), 6.62–7.08 (m, 20H, CH); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 9.96$ (s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $[\text{D}_6]\text{benzene}$, 293 K): $\delta = 31.66$ (s, CHPh), 44.25 (s, CHPh), 123.08, 124.90, 126.70, 127.30, 129.45, 130.22 (all s, CH), 145.30, 140.41 (s, C).

4 and 5: A solution of complex **2** or **3**, respectively, in acetone/acetonitrile (0.10 mmol, 5 mL) was treated with $[\text{FeCp}_2](\text{CF}_3\text{SO}_3)$ (0.20 mmol). After the color of the solution changed from red to yellow, the solution was evaporated to dryness and the residue treated with diethyl ether. A yellow solid was obtained by separation from the liquid by decantation and washing with diethyl ether. **4:** Yield 104 mg, 78%; ^1H NMR (300 MHz, $[\text{D}_6]\text{acetone}$, 293 K): $\delta = -20.14$ (dd, $J(\text{H,P}) = 7.8$, 3.3 Hz, 1H, Ir-H-Ir), -0.42 (d, $J(\text{H,H}) = 6.6$ Hz, CH_3), 1.70 (s, 3H, NCCH_3), 2.85 (s, 3H, NCCH_3), 2.88 (m, 1H, CH_2), 4.08 (dd, $J(\text{H,H}) = 5.1$, 1.5 Hz, 1H, CH_2), 4.64 (m, 1H, CH), 4.83 (dq, $J(\text{H,H}) = 6.6$, 6.3 Hz, 1H, CH), 5.35 (br, 1H, NH), 6.66 (br, 1H, NH); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $[\text{D}_6]\text{acetone}$, 293 K): $\delta = 3.41$ (s), 11.78 (s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $[\text{D}_6]\text{acetone}$, 293 K): $\delta = 1.48$ (s, NCCH_3), 4.21 (s, NCCH_3), 14.14 (s, CH_3), 40.66 (s, CH), 42.31 (s, CH_2),

81.15 (s, CH), 121.79 (s, NCCH_3), 122.06 (s, NCCH_3), 122.41 (q, $J(\text{C,F}) = 322.4$ Hz, CF_3SO_3). **5:** Yield 96 mg, 64%; ^1H NMR (300 MHz, CD_2Cl_2 , 293 K): $\delta = -17.86$ (dd, $J(\text{H,P}) = 49.5$, 11.1 Hz, 1H, Ir-H-Ir), 1.03 (s, 3H, NCCH_3), 2.55 (s, 3H, NCCH_3), 2.90 (s, 3H, NCCH_3), 5.76 (br, 1H, NH), 6.15 (br, 1H, NH), 6.70 (d, $J(\text{H,H}) = 7.2$ Hz, 2H, CH), 6.86 (s, 1H, -CH), 6.91 (t, $J(\text{H,H}) = 7.2$ Hz, 1H, CH), 6.95 (d, $J(\text{H,H}) = 7.5$ Hz, 2H, CH), 7.00 (t, $J(\text{H,H}) = 7.2$ Hz, 2H, CH), 7.05 (t, $J(\text{H,H}) = 7.2$ Hz, 1H, CH), 7.15 (dd, $J(\text{H,H}) = 7.5$, 7.2 Hz, 2H, CH). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $[\text{D}_6]\text{acetone}$, 293 K): $\delta = 14.15$ (s), 17.15 (s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CD_2Cl_2 , 293 K): $\delta = 1.58$ (s, NCCH_3), 4.75 (s, NCCH_3), 5.20 (s, NCCH_3), 117.53 (s, NCCH_3), 121.34 (s, NCCH_3), 123.52 (s, NCCH_3), 125.49, 125.63, 127.92, 128.25, 128.78, 129.11 (all s, CH), 133.40 (d, $J(\text{C,P}) = 7.1$ Hz, Ir-C), 141.09 (s, C), 141.92 (s, =CH), 148.84 (s, C).

Received: October 18, 2001 [Z18080]

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- A crystallographic imposed two-fold symmetry was observed relating the two halves of the dinuclear complex. Crystal data for **2**: $\text{C}_{36}\text{H}_{66}\text{Ir}_2\text{N}_2\text{P}_2$, $M_r = 973.24$, truncated octahedron ($0.21 \times 0.24 \times 0.28$ mm), orthorhombic, space group $Pbcn$, $a = 17.0149(13)$, $b = 15.7320(12)$, $c = 14.0527(11)$ Å, $V = 3761.6(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.719$ g cm⁻³, $F(000) = 1920$, $T = 173(2)$ K, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å, $\mu = 7.179$ mm⁻¹). Bruker SMART APEX CCD diffractometer. 22837 measured reflections (2θ : 3.5–57.2°, ω scans 0.3°), 4570 unique ($R_{\text{int}} = 0.0576$); multiscan absorption correction applied (SADABS program), with min/max. trans. factors 0.176/0.254. Structure solved by Patterson and difference-Fourier maps; refined using SHELXTL. Final agreement factors were $R1 = 0.0283$ (3608 observed reflections, $F^2 > 4\sigma(F^2)$) and $wR2 = 0.0543$; data/restraints/parameters 4570/0/215; GoF = 0.972. Largest peak and hole 0.98 and -1.53 e Å⁻³. CCDC-169454 (**2**) and -169455 (**4**) 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 (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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- Crystal data for **4** $0.5\text{C}_4\text{H}_{10}\text{O} \cdot \text{C}_{38}\text{H}_{64}\text{F}_{6}\text{Ir}_2\text{N}_4\text{O}_6\text{P}_2\text{S}_2 \cdot 0.5\text{C}_4\text{H}_{10}\text{O}$, $M_r = 1334.45$, monoclinic, $P2_1/n$, $a = 12.1052(9)$, $b = 22.6941(17)$, $c = 20.0793(15)$ Å, $\beta = 97.820(1)^\circ$, $V = 5464.8(7)$ Å³, $Z = 4$, $\rho_{\text{calcd}} =$

1.622 g cm⁻³, $F(000) = 2636$, $\mu = 5.064$ mm⁻¹. Data collected as described for **2** with an irregular block (0.35 × 0.19 × 0.08 mm). 35819 measured reflections, 12913 unique; a multiscan absorption correction was performed (SADABS program), with min./max. trans. factors 0.421/0.727. Structure solution and refinement as described for **2**. Final agreement factors were $R1 = 0.0520$ (8227 observed reflections) and $wR2 = 0.1088$. Data/restraints/parameters 12913/7/631; GoF = 0.949. Largest peak and 2.358 and -1.238 e Å⁻³.

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Bis(1,2,3,4- η^4 -anthracene)cobaltate(1 –)**

William W. Brennessel, Victor G. Young, Jr., and John E. Ellis*

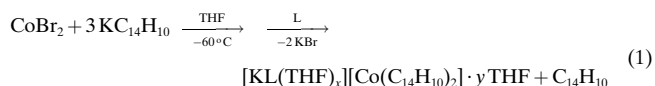
Dedicated to Professor Klaus Jonas

Polycyclic aromatic hydrocarbon (PAH or polyarene)^[1] anion mediated reductions of transition metal halides and related substances provide convenient and sometimes unique routes to a variety of polyarene metal complexes and derived species.^[2] Since the polyarene ligands may be labile and easily displaced by a variety of small molecules, polyarene metal complexes are potential sources of highly unsaturated metallic units in chemical synthesis.^[3] Homoleptic systems are of particular interest since these species may function as “naked” metal atom reagents and are therefore valuable precursors for the general exploration of low-valent transition metal chemistry.^[4] Except for the first reported homoleptic polyarene transition metal complex [Ru(C₁₀H₈)₂]²⁺ (C₁₀H₈ = naphthalene),^[5] all previous examples contained only early (Groups 4–6) transition metals.^[4] However, the existence of this cationic ruthenium species suggested that related neutral and anionic polyarene complexes of later transition metals should also be accessible. We now report on the first anion of this type and the initial homoleptic polyarene complex of cobalt, bis(η^4 -anthracene)cobaltate(1 –) (**1**). The only previously known homoleptic anthracene transition metal complex is bis(anthracene)chromium(0), which was prepared by the reaction of chromium vapor and anthracene in a metal atom reactor.^[4c]

[*] Prof. J. E. Ellis, W. W. Brennessel, Dr. V. G. Young, Jr.
 Department of Chemistry
 University of Minnesota
 Minneapolis, Minnesota 55455 (USA)
 Fax: (+1) 612-626-7541
 E-mail: ellis@chem.umn.edu

[**] Highly Reduced Organometallics, part 56. This work was supported by the U.S. National Science Foundation and the donors of the Petroleum Research Fund, Administered by the American Chemical Society. We thank Ms. Christine Lundby for expert assistance in the preparation of this manuscript. Part 55: J. M. Allen, W. W. Brennessel, C. E. Buss, J. E. Ellis, M. E. Minyaev, M. Pink, G. F. Warnock, M. L. Winzenburg, V. G. Young, Jr., *Inorg. Chem.* **2001**, *40*, 5279.

Reduction of cobalt(II) bromide by three equivalents of potassium anthracene in tetrahydrofuran (THF) at –55 to –65 °C provided a dark red solution, from which deep red, nearly black, microcrystals of **1** as [K([2.2.2]cryptand)]⁺ or [K([18]crown-6)(THF)₂]⁺ salts were isolated in 82–87 % yields (see Experimental Section for details; [Eq. (1)]). Corresponding reductions conducted with alkali metal naphthalenes provided much less thermally stable solutions of a presumably analogous bis(naphthalene)cobaltate(1 –).



1a: L = [2.2.2]cryptand, $x = 0$; $y = 1/2$; 82 %

1b: L = [18]crown-6, $x = 2$; $y = 0$; 87 %

Although this substance is highly reactive towards a number of substrates, for example, it readily reacts with carbon monoxide at normal pressures and –60 °C to produce [Co(CO)₄][–], all attempts to isolate this interesting species have so far failed.^[6] Interestingly, the reduction of cobaltocene by three equivalents of potassium naphthalene provided a similarly labile source of Co^{1–}, which also defied isolation and characterization.^[7]

¹H and ¹³C NMR spectra of **1** were independent of the cation and established that its stoichiometry in solution is identical to that observed in the solid state (vide infra). ¹H, ¹³C correlated NMR spectra of **1** exhibited two equally intense quaternary ¹³C signals at $\delta = 134.1$ and 146.0, which are indicative of two equivalent η^4 -anthracenes bound through one peripheral ring each to cobalt.^[8] ¹H NMR spectra of **1** are also consistent with the presence of two identical anthracene groups bound in the same fashion to cobalt (see Experimental Section). These resonance positions and patterns are consistent with those previously observed for other η^4 -anthracene transition metal complexes,^[9] and provide compelling evidence for the presence of discrete bis(1,2,3,4- η^4 -anthracene)cobaltate(1 –) units in solution.

Single-crystal X-ray studies on **1a** and **1b** were carried out^[10] and confirmed the formulation of **1** based on NMR data and elemental analyses. The cations in these salts are unexceptional and well separated from anions in the crystalline lattices. Since the structures of **1** in both salts show nearly identical features, but the cobaltate in **1a** suffered from slight disorder in one anthracene ring, only **1b** will be described herein. The coordination environment about the cobalt is distorted tetrahedral, as defined by midpoints of the outer C–C bonds of the coordinated diene units (Figure 1), and resembles that previously observed in [Co(η^4 -1,4-di-*tert*-butylbuta-1,3-diene)₂][–] (**2**).^[11] Analogous Co–C and C–C distances of the cobalt-diene units in **1b** and **2** are also very similar, suggesting that the Co–C interactions in both species are closely related. For example, the respective C–C distances of the coordinated diene units in **1b** and **2** show no significant variation.^[12] This situation is typical of later transition metal conjugated diene complexes, such as the d⁸ Fe⁰ complex, η^4 -butadiene iron tricarbonyl,^[13] in which metal π donation (backbonding) is not so important as it is in related early

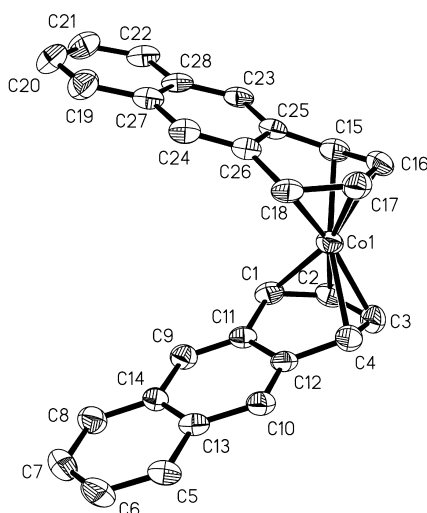
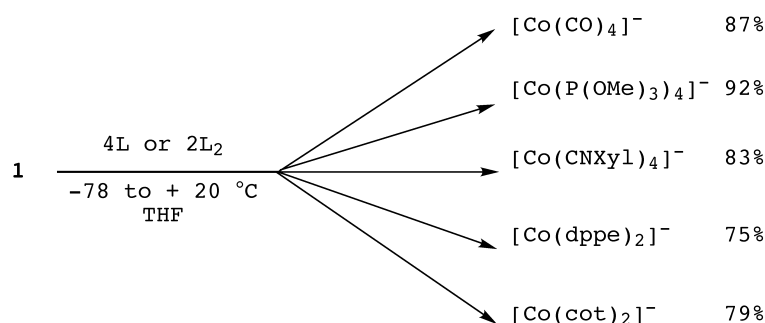


Figure 1. Molecular structure of the anion in **1b**. Thermal ellipsoids are set at the 50% probability level, with hydrogen atoms omitted for clarity. Important dimensions [$\text{\AA}$ and $^\circ$]: Co1–C1 2.125(4), Co1–C2 1.978(4), Co1–C3 2.011(4), Co1–C4 2.132(4), Co1–C15 2.154(4), Co1–C16 2.010(4), Co1–C17 1.974(4), Co1–C18 2.112(4), C1–C2 1.406(5), C2–C3 1.424(5), C3–C4 1.422(5), C15–C16 1.413(5), C16–C17 1.416(5), C17–C18 1.422(5), Co-centroid(η^4) 1.64; centroid(η^4)–Co-centroid(η^4) 172.5.

transition metal dienes.^[14] Another measure of metal π donation in cyclic η^4 -diene complexes is the magnitude of the dihedral (or fold) angle, defined by the intersection of the planes of the η^4 -diene and the uncoordinated group attached to the outer diene carbon atoms,^[15] that is, the exo-naphthalene unit in the case of η^4 -anthracene complexes. In **1b** this angle is 27.8° and similar to the one of 26.2° found in the formally Ni^0 complex $[\text{Ni}(\eta^4\text{-C}_{14}\text{H}_{10})(\eta^2\text{-Et}_2\text{PCH}_2\text{CH}_2\text{-PEt}_2)]$.^[16] In contrast, early transition metal η^4 -anthracene complexes have significantly larger dihedral angles,^[17] which is indicative of a greater degree of metal to anthracene back-bonding than that present in the cobalt or nickel species. For these reasons, as in the case of **2**,^[11] **1** appears to be best formulated as a substituted conjugated diene complex of d^{10} Co(I-) .

Although certain η^4 -anthracene complexes, notably $[\text{Ta}(\eta^4\text{-C}_{14}\text{H}_{10})(\text{dmpe})_2\text{Cl}]$ ($\text{dmpe} = 1,2\text{-bis(dimethylphosphanyl)ethane}$),^[9c] and $[\text{Co}(\eta^4\text{-C}_{14}\text{H}_{10})(\text{PMe}_3)_2(\text{SnPh}_3)]$ ^[18] are inert towards carbon monoxide under normal conditions, solutions of **1** in THF readily absorb CO at atmospheric pressure and temperatures $\geq -30^\circ\text{C}$ to give high yields (87%) of $[\text{Co}(\text{CO})_4]^-$. To further establish the utility of **1** as a precursor to low-valent cobalt complexes, it was treated with a variety of ligands, including 2,6-dimethylphenyl isocyanide (CNXyl), trimethylphosphite (P(OMe)_3), 1,2-bis(diphenylphosphanyl)ethane (dppe), and 1,3,5,7-cyclooctatetraene (cot) as shown in Scheme 1. All reactions proceeded completely within minutes at temperatures $\geq -30^\circ\text{C}$ to provide the respective $[\text{CoL}_4]^-$ ($\text{L} = \text{CNXyl}$, P(OMe)_3) or $[\text{CoL}_2]^-$ ($\text{L} = \text{dppe}$ or cot) in 75–92% yields. While $[\text{Co}(\text{CNXyl})_4]^-$ ^[7] and $[\text{Co}(\text{P(OMe)}_3)_4]^-$ ^[19] have been fully characterized previously, $[\text{Co}(\text{dppe})_2]^-$ (**3**) has been only identified in solution by cyclic voltammetry,^[20] and $[\text{Co}(\text{cot})_2]^-$, **4**, is a new substance and the first homoleptic cot complex of cobalt. Single-crystal X-ray studies of **3** and **4** were carried out to confirm their natures. Cations were well



Scheme 1. Reactions of **1** with $\text{L} = \text{CO}$ (1 atm P), P(OMe)_3 , CNXyl, and $\text{L}_2 = \text{dppe}$, cot, with isolated percentage yields of products.

separated from the anions in these salts and appeared to have no significant influence on the structures of **3** and **4**.^[21, 10b]

Deep red **3** is the first structurally characterized homoleptic triorganophosphanecobaltate(1–),^[22] and has a slightly distorted tetrahedral geometry about the cobalt center (Figure 2) similar to that recently reported for $[\text{Co}(\eta^2\text{-tmbp})_2]^-$ ($\text{tmbp} = 4,4',5,5'\text{-tetramethyl-2,2'-biphosphinine}$).^[23] For example, **3** has a twist angle, θ , between planes, defined by the

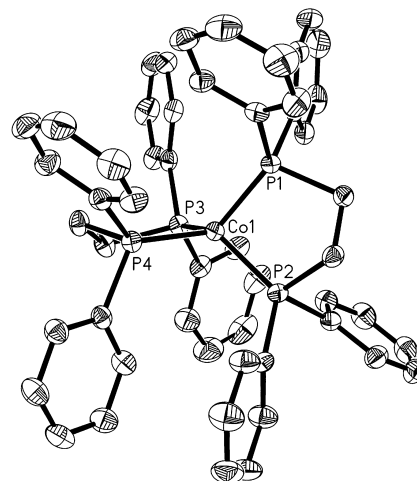


Figure 2. Molecular structure of **3**, cation not shown. Thermal ellipsoids are set at the 50% probability level, with hydrogen atoms omitted for clarity. Important dimensions [$\text{\AA}$ and $^\circ$]: Co1–P1 2.1124(5), Co1–P2 2.1156(6), Co1–P3 2.1045(5), Co1–P4 2.1037(5), P–C_{av} for phenyl carbon atoms 1.86(1), P–C_{av} for ethane carbon atoms 1.873(6); P1–Co1–P2 89.14(2), P3–Co1–P4 89.86(2).

two CoP_2 units, of 85° , where $\theta = 90^\circ$ would correspond to tetrahedral coordination, while those observed for two independent anions in the biphosphinine complex are $\theta = 78$ and 83° . Also, average Co–P distances in these two cobaltates, both of which are best formulated as a d^{10} Co^- species, are experimentally indistinguishable, that is, 2.109(6) $\text{\AA}$ for **3** and 2.100(11) $\text{\AA}$ for the biphosphinine complex.

Deep green **4** is noteworthy in that it represents only the third well-characterized anionic homoleptic cot transition metal complex,^[24] which is surprising in view of the good acceptor ability of this ligand. To our knowledge, the only other structurally authenticated homoleptic cot complexes of the later (Groups 7–11) transition metals are $[\text{Fe}(\text{cot})_2]$,^[25] $[\text{Ru}(\text{cot})_2]$,^[26] and $[\text{Ag}(\text{cot})]^+$.^[27] Although attempts to prepare neutral homoleptic cot complexes of cobalt (by metal

vapor syntheses) were unsuccessful,^[28] two nickel species are well characterized, $[\text{Ni}(\text{cot})_2]$ and $[\text{Ni}(\text{cot})_2]$.^[29a] Related phenylcyclooctatetraene (Phcot) nickel complexes have been structurally characterized, that is, $[\text{Ni}(\text{Phcot})_2]$ and $[\text{Ni}(\text{Phcot})_2]$, where the latter contains the tetrahedral coordination about nickel expected of $\text{d}^{10} \text{Ni}^0$.^[29b] Solutions of **4** in tetrahydrofuran and acetonitrile had virtually identical ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR solution spectra and showed sharp singlets at $\delta_{\text{H}} = 5.18$ and $\delta_{\text{C}} = 91.0$, respectively, with $J_{\text{C,H}} = 149.7$ Hz. These spectra were temperature independent (down to -80°C in $[\text{D}_8]\text{THF}$) and indicate that **4** is highly fluxional, as are all other known η^4 -cot complexes.^[30] The δ_{C} and $J_{\text{C,H}}$ values for **4** are intermediate between those of free cot, $\delta_{\text{C}} = 132.7$ and $J_{\text{C,H}} = 154.4$ Hz, and cot^{2-} (as K^+ salt), $\delta_{\text{C}} = 89.9$ and $J_{\text{C,H}} = 143.3$ Hz,^[31] and suggest that the coordinated cot groups in **4** remove substantial electron density from cobalt.

An X-ray structural analysis also indicates that the η^4 -cot groups in **4** function as substantially better acceptor ligands than the η^4 -diene units in **1b** and **2** (Figure 3). For example, the distinctive long–short–long pattern in the C–C lengths of the coordinated diene unit in **4** is absent in **1b** and **2**, and

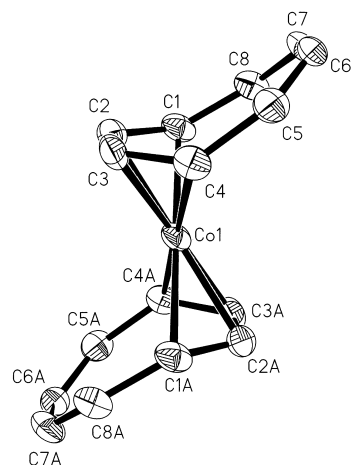


Figure 3. Molecular structure of **4**, cation not shown. Thermal ellipsoids are set at the 50% probability level, with hydrogen atoms omitted for clarity. Important dimensions [$\text{\AA}$ and $^\circ$]: Co1–C1 2.152(3), Co1–C2 1.991(3), Co1–C3 1.989(3), Co1–C4 2.199(3), C1–C2 1.429(4), C2–C3 1.398(4), C3–C4 1.437(4), C4–C5 1.454(4), C5–C6 1.364(4), C6–C7 1.405(4), C7–C8 1.383(4), C1–C8 1.447(4), Co1–centroid(η^4) 1.61, centroid(η^4)–Co–centroid(η^4) 180° .

suggests that there is a significant metallacyclopentene or $\sigma^2\pi$ contribution to the cobalt–cot bonding.^[13] The relatively large dihedral angle of 38.6° ^[15] of the cot ligands in **4**, compared to the corresponding 27.8° angle present in **1b**, is also in accord with this view. However, the most persuasive evidence that the cot groups in **4** are superb acceptors is the surprising *planar* geometry observed for cobalt, which is consistent with the presence of $\text{d}^8 \text{Co}^{\text{I}}$, in contrast to the corresponding tetrahedral geometry of cobalt in **1b**, indicative of $\text{d}^{10} \text{Co}^{\text{I}}$.^[32] The interaction of **1** with two equivalents of cot to give **4** may be regarded as a reaction in which each cot ligand functions formally as a one-electron oxidizing agent. However, the highly nonplanar η^4 -cot ligand in **4** is substantially different in character from the recently reported planar η^2 -cot ligands in formal $\text{d}^{10} \text{Ni}^0$ complexes, for example, $[\text{Ni}(\eta^2$ -

$\text{cot})(\eta^2\text{-iPr}_2\text{PCH}_2\text{CH}_2\text{PiPr}_2)]$, which are formulated to contain semiaromatic planar C_8H_8 radical anions.^[31] Both this latter report and our results demonstrate that coordinated cot, *regardless of its geometry or hapticity*, is able to function as an outstanding acceptor in later transition metal chemistry.

In summary, we have established the existence of the first homoleptic polyarene complex of cobalt, bis(1,2,3,4- η^4 -anthracene)cobaltate(1 $-$), and have shown that it functions as an effective and facile source of “naked” atomic cobalt anion, $\text{Co}^{\text{I-}}$, in several reactions. In this regard, **1** is related to $[\text{Co}(\text{C}_2\text{H}_4)_4]^-$ and $[\text{Co}(1,5\text{-cyclooctadiene})_2]^-$, prepared and studied by Klaus Jonas more than 20 years ago.^[33] Extensions of this investigation to other polyarenes and later transition metals are currently in progress in this laboratory.

Experimental Section

1a: A solution of anhydrous CoBr_2 (0.528 g, 2.42 mmol) in THF (100 mL, -78°C) was added by cannula to a magnetically stirred solution of $\text{KC}_{14}\text{H}_{10}$ (7.24 mmol) in THF (100 mL, -78°C), containing a slight excess of anthracene (1.2 mmol). The reaction mixture turned deep red during the transfer and was slowly warmed to 20°C over a 12 h period, and then filtered into a vessel containing a solution of [2.2.2]cryptand (1.00 g, 2.66 mmol) in THF (50 mL). The filtrate was stirred for 2 h at 20°C and then heptane (30 mL) was added. After all but about 30 mL of solvent mixture was removed in vacuo, diethyl ether (75 mL) was added, whereupon a dark solid formed. The latter was thoroughly washed with diethyl ether (40 mL) and pentane (2×40 mL) to remove anthracene, dried in vacuo, and recrystallized from THF/diethyl ether to provide satisfactorily pure deep red-black microcrystalline **1a** (1.72 g; 82% based on CoBr_2). Elemental analysis calcd for $\text{C}_{48}\text{H}_{60}\text{CoKN}_2\text{O}_{6.5}$ (%): C 66.49, H 6.98, N 3.23; found: C 66.05, H 7.09, N 2.89; m.p. $131\text{--}132^\circ\text{C}$ (decomp); ^1H NMR (300 MHz $[\text{D}_8]\text{THF}$, 20°C , THF and [2.2.2]cryptand resonances omitted): $\delta = 3.07$ (br m, 4H; $\text{H}_{1,4}$), 5.06 (br m, 4H; $\text{H}_{2,3}$), 6.64 (m, 4H; $\text{H}_{5,8}$ or $\text{H}_{6,7}$), 6.87 (m, 4H; $\text{H}_{6,7}$ or $\text{H}_{5,8}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.4 MHz, $[\text{D}_8]\text{THF}$, 20°C , THF and [2.2.2]cryptand resonances omitted): $\delta = 108.8$ (s; $\text{C}_{9,10}$), 121.2 (s; $\text{C}_{5,8}$ or $\text{C}_{6,7}$), 124.7 (s; $\text{C}_{6,7}$ or $\text{C}_{5,8}$), 134.1 (s; $\text{C}_{13,14}$), 146.0 (s; $\text{C}_{11,12}$). The metal-coordinated carbon atoms could not be resolved. Assignment of C,H resonances was established by ^1H – ^{13}C heteronuclear multiple quantum correlation (HMQC) and trends previously established for η^4 -anthracene or naphthalene complexes,^[2,8] but no unique assignment of $\text{C}_{5,8}$, $\text{C}_{6,7}$, or corresponding hydrogen atoms was possible. X-ray quality single crystals of **1a** were grown as deep red-black blocks from pentane–THF at 0°C for 24 h under an argon atmosphere.

1b: By essentially the same procedure as described for **1a**, reduction of CoBr_2 (0.507 g, 2.32 mmol) by $\text{KC}_{14}\text{H}_{10}$ (6.95 mmol), followed by addition of [18]crown-6 (0.674 g, 2.55 mmol), work up and recrystallization provided satisfactorily pure deep red microcrystalline **1b** (1.74 g; 87% based on CoBr_2). Elemental analysis calcd for $\text{C}_{48}\text{H}_{60}\text{CoK}_2\text{O}_8$ (%): C 67.04, H 7.03; found: C 66.41, H 6.65; m.p. $139\text{--}140^\circ\text{C}$ (decomp). NMR spectral properties of **1b** were identical for those of **1a**, except for absorptions due to cations. X-ray quality single crystals of **1b** were grown as red-black needles from pentane–THF at 0°C for 24 h under an argon atmosphere.

3: A solution of dppe (0.508 g, 1.28 mmol) in cold THF (70 mL, -78°C) was added by cannula to **1b** (0.500 g, 0.579 mmol) in THF (30 mL, -78°C). Upon slowly warming with stirring, the solution first changed from dark red to deep green at about -30°C . After further stirring at room temperature for 6 h it assumed the deep red hue of **3**. After filtration, heptane (40 mL) was added and all but about 40 mL of solvent mixture was removed in vacuo. Additional heptane (80 mL) was added to completely precipitate the product, which was separated by filtration, washed with pentane (2×20 mL) and dried in vacuo to provide magenta microcrystals of **3** (0.538 g; 75% yield based on **1b**). Elemental analysis calcd for $\text{C}_{68}\text{H}_{80}\text{CoK}_2\text{O}_7\text{P}_4$ (%): C 66.33, H 6.55; found: C 66.54, H 6.57; m.p. $216\text{--}218^\circ\text{C}$ (decomp). ^1H NMR (300 MHz, $[\text{D}_8]\text{THF}$, 20°C , THF and [18]crown-6 resonances omitted): $\delta = 7.27$ (br m, 16H; C_6H_5 of dppe), 6.70 (br m, 24H; C_6H_5 of dppe), 1.94 (br m, 8H; C_2H_4 of dppe); $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, $[\text{D}_8]\text{THF}$, 20°C , ref: 85% H_3PO_4): $\delta = 72.3$ (br, dppe).

4: Excess cot (0.5 mL) in cold THF (20 mL, -78°C) was added by cannula to a deep red solution of **1a** (0.317 g, 0.366 mmol) in cold THF (60 mL, -78°C). The reaction mixture slowly warmed to room temperature over a period of about 12 h. At about -30° , the color changed to a deep green. Following filtration at room temperature, the solvent was removed in vacuo. Addition of pentane (150 mL) and subsequent washing with pentane (30 mL) provided deep green-black microcrystalline **4** (0.198 g; 79% yield based on **1a**). Elemental analysis calcd for $\text{C}_{34}\text{H}_{52}\text{CoKN}_2\text{O}_6$ (%): C 59.81, H 7.68, N 4.10; found: C 60.47, H 7.36, N 3.90; m.p. $175-177^{\circ}\text{C}$ (decomp); ^1H NMR (300 MHz, $[\text{D}_8]\text{THF}$, 20°C): $\delta = 5.18$ (s, 16H), 3.34 (br, 24H, cryptand), 2.36 (br, 12H, cryptand); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, $[\text{D}_8]\text{THF}$, 20°C): $\delta = 91.0$ (s, C_5H_8), 71.3 (s, cryptand), 68.5 (s, cryptand), 54.9 (s, cryptand).

Received: November 26, 2001 [Z18269]

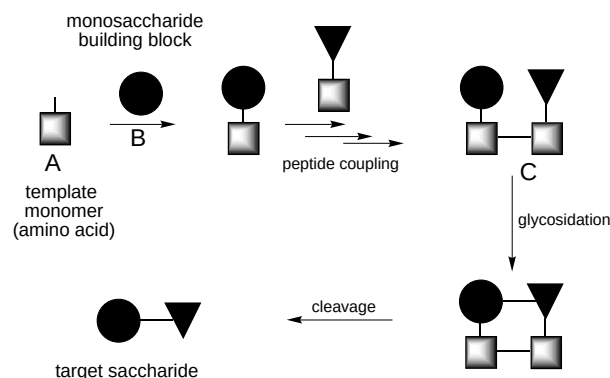
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Peptide-Templated Saccharide Synthesis on a Solid Support**

David R. Greenwell, Abdel F. Ibnouzaki, and Stuart L. Warriner*

The chemical synthesis of oligosaccharides remains a major challenge in synthetic chemistry. Of particular importance is the development of new strategies for the stereoselective synthesis of oligosaccharides and the incorporation of these methods into the overall process of the assembly of target glycosides. Following the pioneering work of Hindsgaul and Barresi^[1] a number of authors have investigated the use of temporary molecular tethers to control the regio- and/or stereoselectivity of glycosidation reactions.^[2, 3] We were intrigued by the possibilities of extending these concepts of tethered intramolecular glycosidation reactions to an overall approach for the synthesis of saccharides. Such an approach requires the challenging construction of a molecular template bearing different monosaccharides at different points along its length. This problem is greatly simplified if the template is based upon a peptide skeleton. In following this strategy a suitably functionalized amino acid **A** is first conjugated to the monosaccharide building blocks **B** through a cleavable linker (Scheme 1). These units are then coupled by means of standard peptide synthesis protocols to provide the suitably



Scheme 1. Peptide-templated saccharide synthesis.

functionalized template **C**. We then envisaged a glycosidation reaction which would “zip up” the carbohydrate with the template and thus control the stereoselectivity of the glycosidation process. The product is then cleaved from the template to furnish the target saccharide.

An additional advantage of using peptide templates is that it should be possible to assemble **C** on solid support by using standard peptide synthesis protocols which opens the door to automation of the whole process. Fairbanks et al. have recently reported on independent studies on the use of peptide tethers to control the solution-phase synthesis of mannose-containing disaccharides.^[4] Here we describe our initial studies of the peptide-templated synthesis of disaccharides on solid support.

The amino acid hydroxyproline (HyP) was chosen as the core of our peptide template as coupling of these units should provide a relatively rigid skeleton. Linkage of the amino acid with the monosaccharide was envisaged by means of a mixed carbonate link between the HyP hydroxy group and the 6-hydroxy group of the sugar unit. Our initial studies focussed on the synthesis of disaccharides by using this methodology, which required the preparation of a peptide template bearing a single glycosyl donor and glycosyl acceptor.

The required building block **3** was prepared in 80 % yield by formation of a mixed carbonate linkage between glucosyl donor **2**^[5] and protected HyP derivative **1**^[6] in phosgene solution (Scheme 2). The room-temperature NMR spectrum of building blocks such as **3** is complicated by the observation of two Fmoc group rotamers in approximately equal quantities. The acceptor unit **5** was prepared in a similar manner by selective coupling of the 6-hydroxy group of the BDA-protected^[7, 8] methyl glucoside **4** with **1** in 81 % yield (Scheme 2; BDA = butanedione-2,3-diacetal). Protection of the secondary hydroxy group was not necessary.

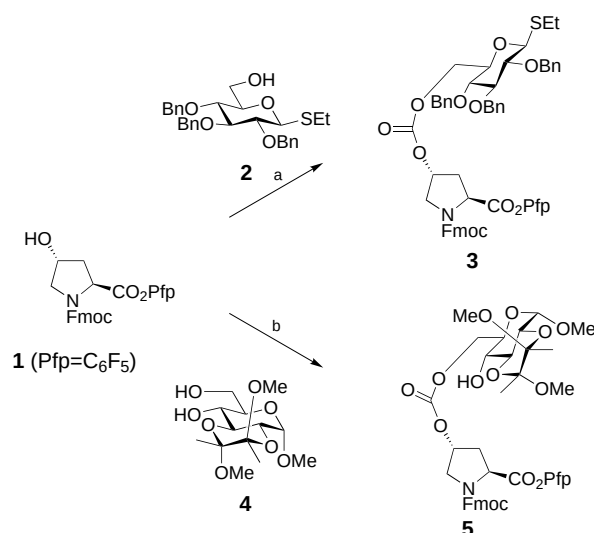
With the required units in hand, we turned our attention to the solid-phase synthesis of the peptide template. As isolation of the final peptide was not required, the peptides were attached directly to an aminomethyl polystyrene-based resin, aminomethyl Novagel,^[9] which had a nominal loading capacity of 0.74 mmol g⁻¹. Peptide synthesis was performed on a semiautomated peptide synthesizer in the presence of 1-hydroxy-7-azabenzotriazole (HOAt).^[10]

The peptide template sequence was initiated by the addition of a glycine unit onto the resin backbone to minimize

[*] Dr. S. L. Warriner, D. R. Greenwell, A. F. Ibnouzaki
School of Chemistry, University of Leeds
Leeds, LS2 9JT (UK)
Fax: (+44) 113-233-6565
E-mail: s.l.warriner@chem.leeds.ac.uk

[**] This work was supported by the Engineering and Physical Sciences Research Council, the University of Leeds, and the Royal Society.

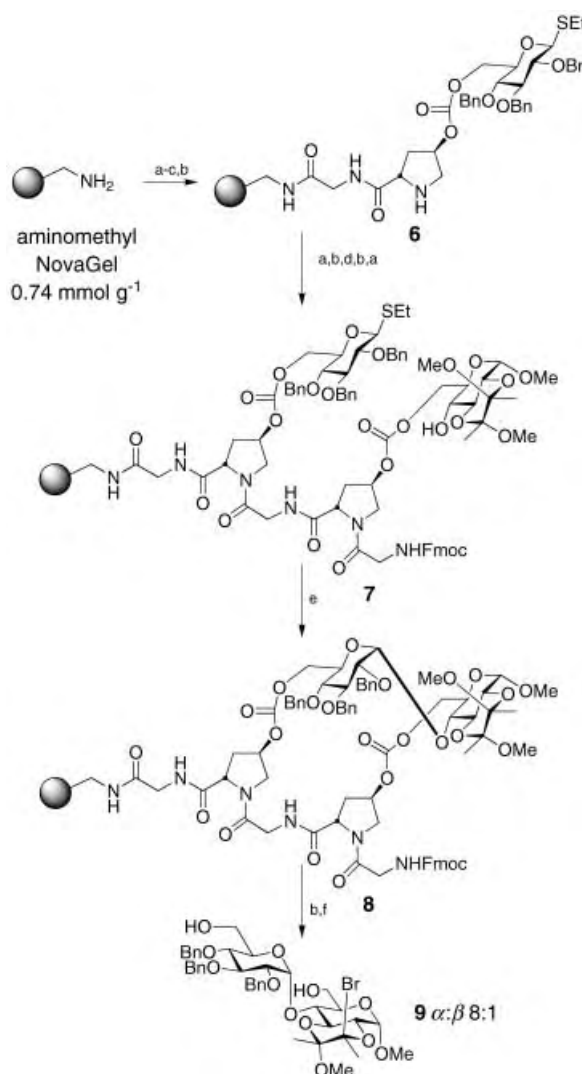
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



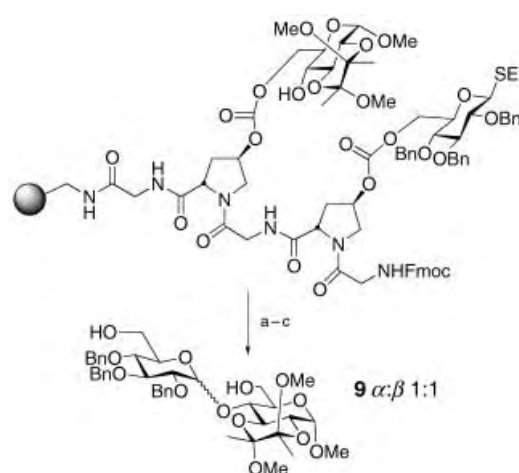
Scheme 2. Preparation of glycosyl donor **3** and glycosyl acceptor **5**. a) COCl_2 , toluene, py, THF, $-78^\circ\text{C} \rightarrow \text{RT}$, then **2**, $-78^\circ\text{C} \rightarrow \text{RT}$, 78%; b) COCl_2 , toluene, THF, **1**, $-78^\circ\text{C} \rightarrow \text{RT}$, then add to **4**, $-78^\circ\text{C} \rightarrow \text{RT}$, 81%. Fmoc = 9-fluorenylmethoxycarbonyl, py = pyridine.

any interactions between the sugars and the polystyrene. The hydroxyproline unit bearing the glycosyl donor building block **3** was then coupled to the resin-bound glycine to give the dipeptide **6** (Scheme 3). Unfortunately, it was not possible to directly couple the acceptor-bearing HyP unit **5** to the proline unit of **6**, presumably because of the steric hindrance of the bulky sugars; however, insertion of an intermediate glycine unit enabled subsequent addition of the acceptor unit **5** and a terminal-protected glycine. The final template structure was hence pentapeptide **7** (Scheme 3) with an alternating HyP-Gly sequence suitably functionalized to form a disaccharide. Fmoc cleavage analysis revealed a final loading of 0.39 mmol g^{-1} . As the loading of the resin is relatively low, any glycoside product must come from intramolecular glycosidation along the template backbone. The dry resin was hence treated with excess of NIS and catalytic amounts of TMSOTf for 16 h. A successful glycosidation reaction would form the 24-membered macrocycle **8**. Following removal of the excess reagents by washing, the terminal Fmoc group was then cleaved by using piperidine in dichloromethane. Cleavage of the carbonate linkage under basic conditions furnished the desired disaccharide **9** in 80% yield (based on a pentapeptide loading of 0.39 mmol g^{-1}) as almost exclusively the α isomer (Scheme 3).

To investigate the influence of the order of addition of the sugar units to the peptide on overall selectivity, the template was resynthesized with the donor and acceptor groups in the opposite order (that is, with the donor towards the N-terminus). The glycosidation reaction once again proceeded smoothly but in this case gave a 75% yield of **9** as a 1:1 mixture of anomers (Scheme 4).^[11] This result clearly demonstrates the influence of the peptide template on the stereoselectivity of the glycosidation process as by simply altering the order of addition the stereoselectivity was dramatically changed. Clearly the conformational preferences of the peptide backbone influence the anomeric selectivity during the glycosidation process.

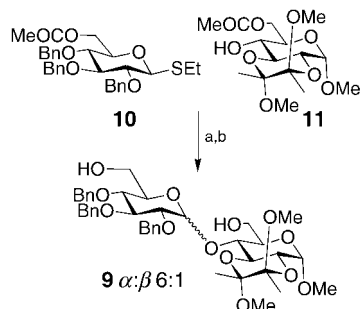


Scheme 3. Synthesis of disaccharide **9** on a peptide template. a) 4 equiv Fmoc-Gly-OPfp, HOAt; b) 20% piperidine, DMF; c) 2.5 equiv **5**, HOAt; d) 2.5 equiv **9** HOAt; e) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF: CH_2Cl_2 4:1, 16 h; f) NaOH, MeOH:THF 4:1, H_2O . DMF = dimethylformamide, NIS = *N*-iodosuccinimide, TMSOTf = trimethylsilyltriethylfluoroborate, MS = molecular sieves.



Scheme 4. Synthesis of disaccharide **9** with the reversed order of glycoside donor and acceptor. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF: CH_2Cl_2 4:1, 16 h; b) 20% piperidine, CH_2Cl_2 ; c) NaOH, MeOH:THF 4:1, H_2O .

The inherent selectivity of the solution-phase intermolecular glycosidations in the absence of a template were ascertained by the coupling of methyl carbonates **10** and **11** (Scheme 5).^[12] Under conditions identical to those employed in the template-based synthesis, disaccharide **9** was formed with an α/β selectivity of 6:1.^[11] It therefore appears that the peptide template increases the α selectivity of the glycosidation when the donor is attached towards the C-terminus of the peptide, while more β anomer is formed when the donor is attached towards the N-terminus.



Scheme 5. Selectivity of coupling in solution. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH₂Cl₂ 4:1, 16 h; b) NaOH, MeOH:THF 4:1, H₂O.

We then explored the applicability of this methodology to the synthesis of a range of disaccharides. In each case the donor **3** remained constant. Glucose-, mannose-, and galactose-based acceptors were synthesized by procedures similar to those employed in the synthesis of **5**, and the subsequent disaccharides synthesized on the peptide template with the glycosyl donor attached at either the N- or C-terminus of the template. Solution-phase glycosidations of the model 6*O*-methoxycarbonyl compounds were also performed to ascertain the inherent selectivities of the glycosidation reactions (Scheme 6).

In all cases, the model solution studies displayed a selectivity of approximately 6:1 in favor of the α isomer (Table 1). In the case of acceptors with the free hydroxy group at the 2-position (to form glucoside **16** and mannoside **17**) the selectivity was more in favor of the β isomer when the reaction

Table 1. Comparison of the yields and selectivities for the synthesis of disaccharides **16–18** according to Scheme 6.

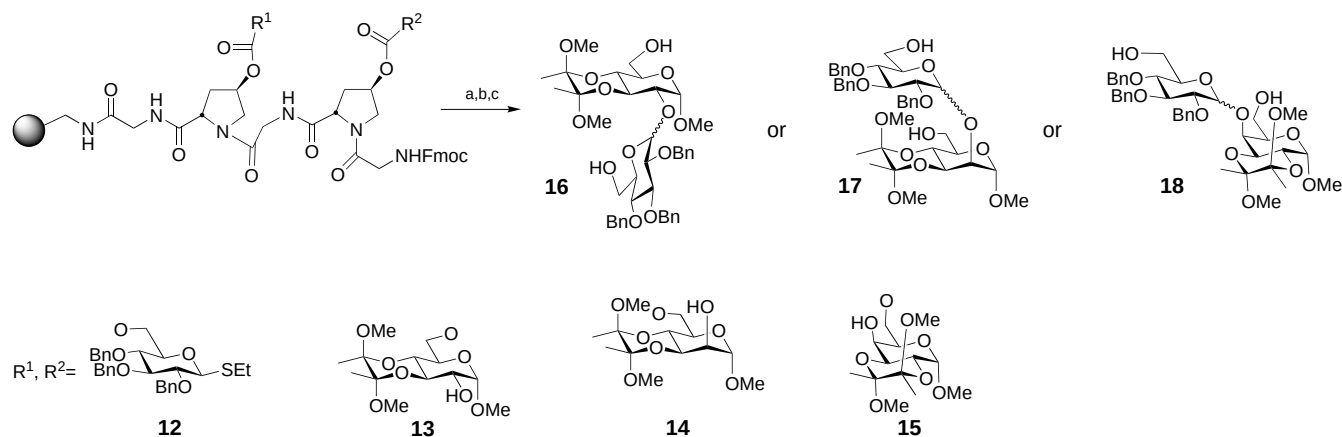
Entry	R ¹	R ²	Product	Yield [%] ^[a]	α/β selectivity support	α/β selectivity solution ^[b]
1	12	13	16	86	2:1	6:1
2	13	12	16	82	2:1	
3	12	14	17	75	2:1	5:1
4	14	12	17	84	2:1	
5	12	15	18	79	1.8:1	7:1
6	15	12	18	81	9:1	

[a] Based on a pentapeptide loading of 0.39 mmol g⁻¹. [b] Solution selectivities were determined by using the 6*O*-methoxycarbonyl-substituted versions of the donor and acceptor in analogy to the reactions shown in Scheme 5.

was performed on the template and was practically invariant of the order of addition of the building blocks (entries 1–4). When the acceptor hydroxy group was located at the 4-position (to form glucoside **9** and galactoside **18**) the selectivity was crucially dependant on the order of addition of the sugars on the template. In contrast to the case of the synthesis of **9** which displays the highest α selectivity when the donor is towards the C-terminus of the template, formation of galactoside **18** gave a 1.8:1 mixture of isomers with the donor towards the C-terminus but a 9:1 mixture of isomers when the donor was at the N-terminus of the template (entries 5 and 6). In all cases the yields of the isolated disaccharides were excellent. We are currently investigating how the conformation of the peptide controls the glycosidation reaction and studying extension of this methodology to the synthesis of larger saccharides.

Experimental Section

9a: Aminomethyl-NovaGel-HL (0.74 mmol g⁻¹, 60 mg, 0.044 mmol) was allowed to swell for 16 h in DMF (1 mL) prior to use. Peptide synthesis was performed on a Milligen 9020 synthesizer by using extended coupling cycles. Fmoc-protected amino acid pentafluorophenyl esters were preactivated with 1-hydroxy-7-azabenzotriazole (HOAt) and added when prompted by the synthesizer. Fmoc-glycine-Pfp (82 mg, 0.176 mmol, 4 equiv) and HOAt (24 mg, 0.176 mmol, 4 equiv) were dissolved in DMF (1 mL), introduced into the synthesizer, and recycled over the resin for 1 h. Following Fmoc removal, **3** (116 mg, 0.11 mmol, 2.5 equiv) and HOAt (15 mg, 0.11 mmol, 2.5 equiv) dissolved in DMF (1 mL) were introduced



Scheme 6. Preparation of several disaccharides on a peptide support. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH₂Cl₂ 4:1, 16 h; b) 20% piperidine, CH₂Cl₂; c) NaOH, MeOH:THF 4:1, H₂O.

and recycled for 1.5 h. This process was repeated for the addition of the next three amino acids, Fmoc-glycine-Pfp, **5**, and Fmoc-glycine-Pfp. After completion of the fifth coupling the resin was washed with CH_2Cl_2 for 15 minutes, and the beads were removed from the synthesizer and dried overnight. 4-Å Molecular sieves (5 beads) and CH_2Cl_2 (1 mL) were added to the resin beads, and the suspension was agitated for 1 h. TfOTMS solution (160 μL of a 16% v/v solution in CH_2Cl_2) was added to a solution of NIS (400 mg, 1.78 mmol in THF (4 mL) and CH_2Cl_2 (1 mL). A 1.25-mL aliquot of the resulting mixture was added to the resin beads, and the suspension was agitated for 18 h. The solution was then removed by filtration, and the resin was washed with CH_2Cl_2 (3×2.5 mL). The resin was treated with 20% piperidine in CH_2Cl_2 (2 mL), and the mixture was agitated for 15 min. The solvent was drained and the resin was washed with CH_2Cl_2 (3×2.5 mL). A solution of NaOH (10 mg, 0.25 mmol) in THF (0.5 mL) and methanol (2 mL) was transferred to the resin beads. The mixture was then agitated for 1 h, after which the solution was filtered from the resin and the filtrate concentrated to dryness under reduced pressure. The crude products were dissolved in CH_2Cl_2 (5 mL), washed with water (2×5 mL), and dried (MgSO_4), and the major α isomer was purified by preparative HPLC on an Alltech Econosil Silica normal-phase preparative column (10 μm , 250×22 mm) with a flow rate of 10 mL min⁻¹ and gradient elution (0 min: hexane 95%, 2-propanol 5%; 20 min: hexane 65%, 2-propanol 35%; then isocratic for 5 min) to give **9a** (14 mg). $R_f = 0.77$ (petroleum:EtOAc, 1:1); $[\alpha]_D^{25} = -5.69$ ($c = 0.67$ in CHCl_3); IR (thin film): $\bar{\nu} = 3494$ (OH), 3057, 3030, 2990, 2942, 1461, 1409 cm⁻¹; ¹H NMR (500 MHz; CDCl_3 , 25 °C, TMS): $\delta = 7.33$ –7.26 (m, 15H; aromatic protons), 5.70 (d, ³ $J(\text{H,H}) = 3.8$ Hz, 1H; H-1), 4.92 (d, ² $J(\text{H,H}) = 10.9$ Hz, 1H; 3OCH_aH_bPh), 4.85 (d, ² $J(\text{H,H}) = 10.9$ Hz, 1H; 3OCH_aH_bPh), 4.84 (d, ² $J(\text{H,H}) = 11.4$ Hz, 1H; 4OCH_aH_bPh), 4.83 (d, ² $J(\text{H,H}) = 12.1$ Hz, 1H; 2OCH_aH_bPh), 4.80 (d, ² $J(\text{H,H}) = 12.1$ Hz, 1H; 2OCH_aH_bPh), 4.71 (d, ³ $J(\text{H,H}) = 3.5$ Hz, 1H; H-1'), 4.59 (d, ² $J(\text{H,H}) = 11.4$ Hz, 1H; 4OCH_aH_bPh), 4.32 (t, ³ $J(\text{H,H}) = 9.4$ Hz, 1H; H-3'), 4.09 (t, ³ $J(\text{H,H}) = 9.4$ Hz, 1H; H-4'), 3.97 (t, ³ $J(\text{H,H}) = 9.0$ Hz, 1H; H-3), 3.91 (dd, ² $J(\text{H,H}) = 12.3$ Hz, ³ $J(\text{H,H}) = 3.0$ Hz, 1H; H-6a'), 3.87 (dd, ² $J(\text{H,H}) = 11.6$ Hz, ³ $J(\text{H,H}) = 2.4$ Hz, 1H; H-6b), 3.83–3.77 (m, 2H; H-6b' & 5), 3.74 (dd, ² $J(\text{H,H}) = 10.3$ Hz, ³ $J(\text{H,H}) = 3.5$ Hz, 1H; H-2'), 3.73–3.69 (m, 1H; H-5), 3.61 (dd, ² $J(\text{H,H}) = 11.6$ Hz, ³ $J(\text{H,H}) = 5.9$ Hz, 1H; H-6a), 3.56 (dd, ² $J(\text{H,H}) = 9.0$ Hz, ³ $J(\text{H,H}) = 3.8$ Hz, 1H; H-2), 3.42 (t, ³ $J(\text{H,H}) = 9.0$ Hz, 1H; H-4), 3.39 (s, 3H; OCH₃), 3.24 (s, 3H; OCH₃), 3.09 (s, 3H; OCH₃), 1.30 (s, 3H; CH₃), 1.22 (s, 3H; CH₃); ¹³C NMR (125 MHz; CDCl_3 , 25 °C, TMS): $\delta = 138.6$ (aromatic C-1), 138.0 (aromatic C-1), 128.5–127.6 (aromatic C-1, 2, 3, 4, 5, 6), 99.7 (C-BDA), 99.3 (C-BDA), 98.0 (C-1'), 97.1 (C-1), 82.0 (C-3), 79.3 (C-2), 78.4 (C-4), 75.6 (3O-CH₂Ph), 75.2 (4O-CH₂Ph), 73.9 (2O-CH₂Ph), 72.2 (C-5), 70.8 (C-5'), 70.3 (C-3'), 69.5 (C-4'), 68.4 (C-2'), 62.2 (C-6), 61.2 (C-6'), 55.0 (C-1-OCH₃), 48.1 (BDA-OCH₃), 48.0 (BDA-OCH₃), 17.8 (BDA-CH₃), 17.7 (BDA-CH₃); MS (ES⁺): m/z (%): 763 (100%) [$M + \text{Na}^+$]; HR-MS: calcd for C₄₀H₅₂O₁₃Na: 763.3306; found: 763.3302.

Received: August 23, 2001

Revised: January 9, 2002 [Z17782]

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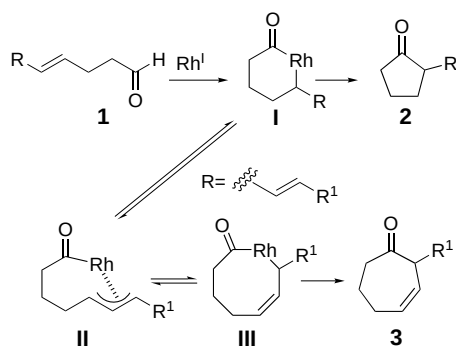
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A New Method for the Synthesis of Cycloheptenones by Rh^I-Catalyzed Intramolecular Hydroacylation of 4,6-Dienals

Yoshihiro Sato, Yoshihiro Oonishi, and Miwako Mori*

The development of methodology for the synthesis of cyclic compounds is important in modern synthetic organic chemistry, not least because there are many biologically active compounds with complicated cyclic structures. The construction of a medium-sized ring is relatively difficult due to unfavorable entropy and nonbonding interactions occurring at the transition state during the cyclization. Transition metal catalyzed cyclization is one of the most promising strategies for the construction of such medium-sized ring compounds.^[1] Rh^I-mediated cyclization of 4-alkenals to give cyclopentanone derivatives was first reported by Sakai et al. in 1972,^[2] and this hydroacylation has subsequently been developed into a catalytic process^[3] and asymmetric reaction.^[4] On the basis of results of mechanistic studies,^[5] it is thought that the reaction proceeds as follows (Scheme 1): a C–H bond of the aldehyde moiety of **1** is oxidatively added to a Rh^I complex followed by insertion of a C=C bond of an olefin to give the rhodacycle intermediate **I**. Reductive elimination from **I** occurs to produce cyclopentanone **2** along with regeneration of the Rh^I complex. We speculated that if a

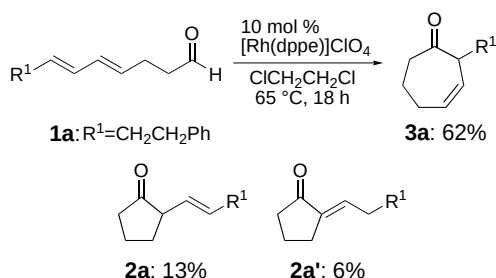
[*] Prof. M. Mori, Dr. Y. Sato, Y. Oonishi
Graduate School of Pharmaceutical Sciences
Hokkaido University
Sapporo 060-0812 (Japan)
Fax: (+81) 11-706-4982
E-mail: mori@pharm.hokudai.ac.jp



Scheme 1. Proposed mechanism of the Rh^I-catalyzed reaction of 4-alkenals to give cyclopentanone derivatives **2** and cycloheptanone derivatives **3**.

double bond is conjugated to a Rh–C bond in rhodacycle **I**, another rhodacycle intermediate **III** would be formed via a π -allylrhodium intermediate **II**. If reductive elimination from **III** occurs, cycloheptanone derivative **3** would be formed. Herein, we report a novel Rh^I-catalyzed cyclization of 4,6-dienals to give a seven-membered-ring compound by a hydroacylation process.^[6]

Initially, we investigated the cyclization of 4,6-dienal **1a** (Scheme 2). Treatment of **1a** with 10 mol % of [Rh(dppe)]ClO₄ (dppe = 1,2-bis(diphenylphosphanyl)ethane), generated in situ from [Rh(nbd)(dppe)]ClO₄ (nbd = norbornadiene)



Scheme 2. Cyclization of 4,6-dienal **1a**.

under an atmosphere of hydrogen,^[3d] in dichloroethane at 65 °C for 18 h gave cycloheptanone **3a** in 62 % yield along with cyclopentanones **2a** and **2a'** in 13 and 6 % yields, respectively. It was thought that cycloheptanone **3a** was produced through reductive elimination from rhodacyclooctenone **III** (see Scheme 1), which was formed from rhodacyclohexanone **I** via π -allylrhodium intermediate **II**. The cyclization of **1a** using other ligands instead of dppe, such as 1,3-bis(diphenylphosphanyl)propane (dppp), 1,2-bis(diphenylphosphanyl)butane (dppb), and PPh₃, gave no or only trace amounts of cyclized products **2a**, **2a'**, and **3a** along with recovery of the starting material **1a** in 54–73 %. Interestingly, the use of (*R*)-BINAP ([1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphane)) in this cyclization gave only **2a** in 75 % yield, although the enantiomeric excess of **2a** was very low (3 % ee).^[7]

Next, the influence of the olefinic geometry of substrate **1a** on the reactivity of this cyclization was carefully examined, and the results are summarized in Table 1. The cyclization of (4*E*,6*E*)-**1a** and that of (4*Z*,6*E*)-**1a**, both of which have an *E*

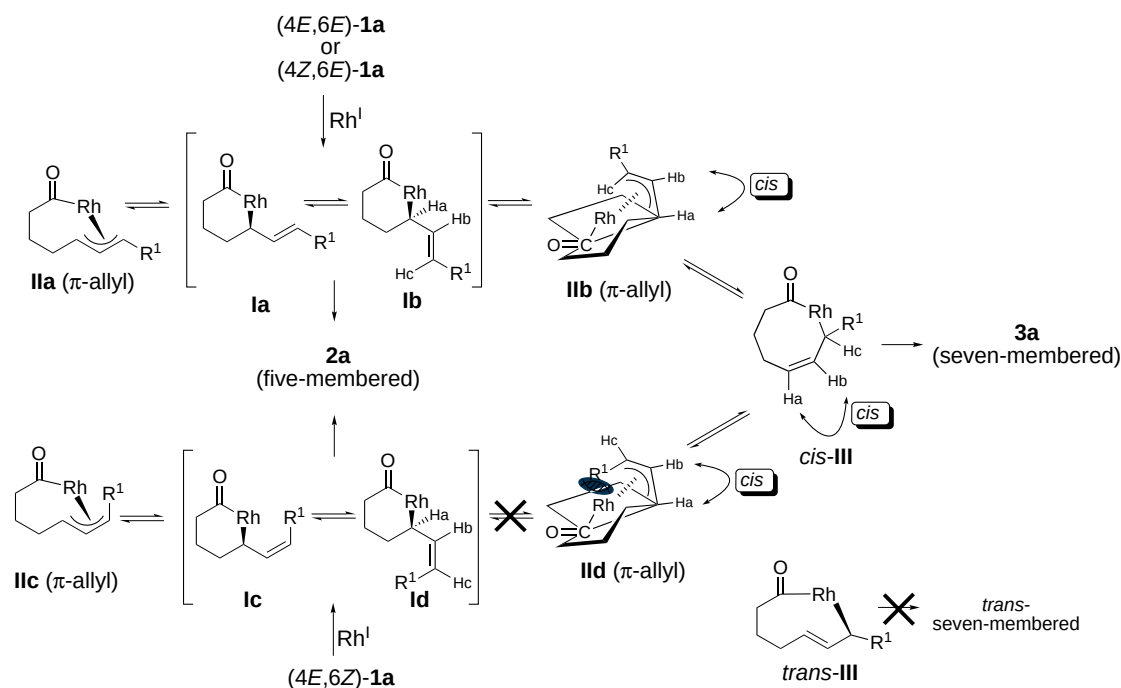
Table 1. Influence of the stereochemistry of **1a** on reactivity.

Substrate	<i>t</i> [h]	3a [%]	2a [%]	2a' [%]	Starting material recovered [%]
(4 <i>E</i> ,6 <i>E</i>)- 1a	18	62	13 ^[a]	6	–
(4 <i>Z</i> ,6 <i>E</i>)- 1a	16	65	11 ^[a]	5	–
(4 <i>E</i> ,6 <i>Z</i>)- 1a	18	trace	49 ^[b]	trace	38

[a] *E* alkene. [b] *Z* alkene.

olefin at the C6 position, gave cycloheptanone **3a** as the major product in 62 and 65 % yields, respectively. On the other hand, the cyclization of (4*E*,6*Z*)-**1a**, which contains a *Z* olefin at the C6 position, gave cyclopentanone **2a** as the major product. These results indicate that the olefinic geometry of the diene moiety in 4,6-dienals strongly affects the reaction course. Thus, the cyclization of substrates with an *E* olefin at the C6 position produced cycloheptanone derivatives as the major product, while a cyclopentanone derivative was obtained from a substrate with a *Z* olefin at the C6 position. A plausible reaction mechanism in accord with these results is outlined in Scheme 3. The reaction of (4*E*,6*E*)-**1a** or (4*Z*,6*E*)-**1a** with a Rh^I catalyst gives rhodacycle intermediates **Ia** and **Ib**, which might be in equilibrium with π -allylrhodium intermediates **IIa** and **IIb**. The cycloheptanone **3a** should be produced through reductive elimination from rhodacyclooctenone *cis*-**III**, while the cyclopentanone **2a** should be formed through reductive elimination from **Ia** or **Ib**. In the cyclization of (4*E*,6*E*)-**1a** and (4*Z*,6*E*)-**1a**, cycloheptanone **3a** was produced in preference to cyclopentanone **2a**. These results indicate that the equilibrium among the intermediates **Ia**, **Ib**, **IIa**, **IIb**, and *cis*-**III** would lie towards *cis*-**III** although the reason is not clear. On the other hand, in the cyclization of (4*E*,6*Z*)-**1a**, rhodacycle intermediates **Ic** and **Id** should be produced (see Scheme 3), which might be also in equilibrium with π -allylrhodium intermediates **IIc** and **IId**. It was thought that π -allylrhodium intermediate **IId** was unstable due to steric repulsion between the R¹ substituent at the C7 position and the rhodium metal center in the complex, resulting in the preferential formation of cyclopentanone **2a** in the cyclization of (4*E*,6*Z*)-**1a**. In all cases, the rhodacyclooctenone *trans*-**III** might be formed via π -allylrhodium intermediate **IIa** or **IIc**. However, it is apparent that a *trans*-seven-membered-ring compound cannot be produced due to its lability.

Cyclization of various 4,6-dienals was investigated under similar conditions (Table 2). The reaction of 4,6-dienal **1b** gave cycloheptanone **3b'** in 66 % yield along with cyclopentanone **2b'** in 9 % yield. In the reaction of **1c**, the cycloheptanone derivatives **3c** and **3c'** were produced in 60 % total yield as the major product. The existence of an olefinic moiety in the side chain is tolerated in this cyclization, and the



Scheme 3. A plausible reaction mechanism that accounts for the different products obtained in the cyclization of **1a**.

Table 2. Cyclization of various dienals.^[a]

Substrate	<i>t</i> [h]	Yield [%]		
1b : $R^1 = \text{cyclohexylmethyl}$	24	3b : –	3b' : 66	2b' : 9
1c ^[b] : $R^1 = \text{benzyloxymethyl}$	24	3c : 45	3c' : 15	2c' : 3
1d ^[c] : $R^1 = \text{1,3-bis(benzyloxymethyl)propyl}$	18	3d : 70	3d' : –	2d' : –
1e ^[d] : $R^1 = \text{H}$	17	3e : 7	3e' : –	2e' ^[e] : 45
1f : $R^1 = \text{cyclopentylmethyl}$	16	2f ^[f] : 60		
1g : $R^2 = \text{CH}_3$	17	3g ^[f] : 10	3g' : 58	2g ^[f] : 18
1h ^[g] : $R^2 = \text{H}$	15	3h : 9	3h' : –	2h ^[h] : 46

[a] All reactions were carried out in the presence of $[\text{Rh}(\text{dppe})]\text{ClO}_4$ (10 mol %) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at 65 °C. [b] Reaction temperature was 45 °C. [c] (4*Z*,6*E*)-**1d** was used as the substrate. [d] The yields were determined by GC. [e] *E/Z* = 1/2.5. [f] The cyclized products were obtained as a single isomer although the stereochemistry has not been determined. [g] The reaction was carried out at 65 °C for 12 h, then at reflux for 3 h. [h] *E/Z* = 1/1.6.

reaction of **1d** gave cycloheptenone **3d** in 70 % yield. On the other hand, the cyclization of **1e** and that of **1f**, having no substituent at the C7 position, gave the cyclopentanone **2e'** and **2f'** in 45 and 60 % yields, respectively, as the major

product. The same tendency was observed in the cyclization of **1g** and **1h**; that is, the cyclization of **1g** under similar conditions gave the bicyclic cycloheptenone derivatives **3g** and **3g'** in 68 % total yield along with bicyclic cyclopentanone **2g'** in 18 % yield, whereas the cyclization of **1h**, having no substituent at the terminus of the diene moiety, preferentially afforded the bicyclic cyclopentanone **2h'**. In all cases, a cycloheptenone derivative should be produced through an unstable eight-membered rhodacycle intermediate such as *cis*-**III** (Scheme 3). It seems likely that a substituent (R^1 or R^2) plays an important role as a donating group to stabilize the buildup of positive charge on the terminal carbon atom of the diene moiety in *cis*-**III**, which might promote the formation of cycloheptenone derivatives.

We have succeeded for the first time in extending Rh^{I} -catalyzed intramolecular hydroacylation to the synthesis of seven-membered rings. The cyclization of 4,6-dienals with a substituent at the C7 position produced cycloheptenone derivatives as the major product, while the cyclization of 4,6-dienals with no substituent at the terminus of the diene moiety preferentially gave cyclopentanone derivatives. The olefinic geometry of the diene moiety in 4,6-dienals also affected the reaction course. Thus, the cyclization of substrates having an *E* olefin at the C6 position produced cycloheptenone derivatives as the major product, while a cyclopentanone derivative was obtained from a substrate with a *Z* olefin at the C6 position. Further studies along this line are in progress.

Experimental Section

Typical procedure for cyclization of (4*E*,6*E*)-**1a**: A solution of $[\text{Rh}(\text{dppe})(\text{nbd})]\text{ClO}_4$ (18.0 mg, 0.026 mmol) in degassed $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.0 mL) was stirred under a H_2 atmosphere at room temperature for 1 h. The reaction vessel was flushed with argon gas, and a solution of (4*E*,6*E*)-

1a (55.0 mg, 0.26 mmol) in degassed $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.6 mL) was added to the mixture. The reaction mixture was stirred at 65 °C for 18 h. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford **3a** (0.16 mmol, 62%) along with **2a** (0.034 mmol, 13%) and **2a'** (0.015 mmol, 6%). Selected spectral data of **3a**: IR (neat): $\tilde{\nu}$ = 3024, 2934, 1708, 1654, 1496, 1456 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.67–1.82 (m, 2H), 2.03–2.18 (m, 2H), 2.31–2.76 (m, 6H), 3.63 (m, 1H) 5.23 (dddd, J = 11.1, 3.2, 2.0, 2.0 Hz, 1H), 5.76 (dddd, J = 11.1, 6.7, 6.7, 1.9 Hz, 1H), 7.16–7.31 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ = 21.8, 29.4, 31.8, 33.2, 44.0, 48.4, 125.7, 125.8, 126.8, 128.2, 128.3, 128.4, 131.2, 141.8, 208.9; EI-LRMS: m/z : 214 [M^+], 123, 110, 104, 91; EI-HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ 214.1358, found 214.1346. **2a**: IR (neat): $\tilde{\nu}$ = 2960, 2854, 1740, 1453, 1149 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.68–1.88 (m, 2H), 2.00–2.42 (m, 6H), 2.68–2.76 (m, 3H), 5.47 (dd, J = 15.6, 6.1 Hz, 1H), 5.60 (dt, J = 15.6, 6.3 Hz, 1H), 7.17–7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ = 20.7, 29.8, 34.4, 35.7, 37.7, 52.2, 125.8, 126.6, 128.2, 128.2, 128.4, 128.4, 132.4, 141.8, 218.9; EI-LRMS: m/z : 214 [M^+], 123, 110, 105, 91; EI-HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ 214.1358, found 214.1362. **2a'**: IR (neat): $\tilde{\nu}$ = 2924, 2856, 1718, 1648, 1096 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.81 (tt, J = 7.6, 7.6 Hz, 2H), 1.93 (dddd, J = 7.6, 7.6, 7.6, 7.6 Hz, 2H), 2.18 (dt, J = 7.6, 7.6 Hz, 2H), 2.34 (dd, J = 7.6, 7.6 Hz, 2H), 2.52–2.57 (m, 2H), 2.67 (t, J = 7.6 Hz, 2H), 6.57 (dddd, J = 7.6, 7.6, 2.7 Hz, 1H), 7.15–7.32 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ = 20.0, 26.9, 29.3, 30.1, 35.6, 38.7, 125.7, 128.1, 128.1, 128.2, 128.2, 135.4, 137.4, 141.5, 206.7; EI-LRMS: m/z : 214 [M^+], 130, 123, 110, 91; EI-HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ 214.1358, found 214.1365.

Received: December 3, 2001 [Z18311]

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Super-Hydrophobic Surface of Aligned Polyacrylonitrile Nanofibers**

Lin Feng, Shuhong Li, Huanjun Li, Jin Zhai, Yanlin Song, Lei Jiang,* and Daoben Zhu

The wettability of solid surfaces is a very important property that is governed by both the chemical composition and the geometrical microstructure of the surface.^[1–3] Super-hydrophobic surfaces, with a water contact angle (CA) greater than 150°, have attracted much interest because of potential practical applications.^[4] Conventionally, super-hydrophobic surfaces have been produced mainly in two ways: One is to create a rough surface (e.g., with a fractal structure)^[5] and the other is to modify the surface with materials of low surface free energy, such as fluorinated or silicon compounds.^[6]

Recently, we have succeeded in preparing densely packed aligned carbon nanotubes (ACNTs).^[7] The water contact angle on this nanostructured ACNT film was $(158.5 \pm 1.5)^\circ$, that is, the ACNT film has super-hydrophobic properties. The water contact angle increased to $(171 \pm 0.5)^\circ$ after modification with a fluoroalkylsilane. This high value is believed to be due to the nanostructure and the presence of fluoroalkylsilane groups. Here we describe a novel method to synthesize aligned polyacrylonitrile (PAN) nanofibers, which have a nanostructure similar to that of the ACNTs but a much lower density. The surface of the as-synthesized PAN nanofibers shows super-hydrophobicity (CA = $(173.8 \pm 1.3)^\circ$). This is the first report of a water contact angle greater than 170° without any modification of the surface. We also note that the density of the aligned nanostructures is very important for the super-hydrophobicity.

Compared with other template syntheses,^[8–10] the method used here to synthesize PAN nanofibers is very simple. Only extrusion of the PAN precursor solution into the solidifying solution under pressure is necessary.^[11] The template was an anodic aluminum oxide membrane, prepared according to ref. [12], with a diameter of 13 mm, a thickness of 60 μm , and a porosity consisting of an array of parallel, straight channels. Aligned nanofibers with different diameters and densities can be easily obtained by using templates with different pore diameters, and the alignment process can be applied to different polymer precursors such as poly(vinyl alcohol), polystyrene, polyesters, and polyamides.

Figure 1a shows a scanning electron microscopic (SEM) image of the surface of the as-prepared anodic aluminum oxide membrane used as template. The pores are arranged in a regular hexagonal pattern with an average pore diameter of

[*] Prof. L. Jiang, Dr. L. Feng, Dr. S. Li, Dr. H. Li, Dr. J. Zhai, Prof. Y. Song, Prof. D. Zhu
Center of Molecular Sciences, Institute of Chemistry
Chinese Academy of Sciences
Beijing 100080 (P.R. China)
Fax: (+86) 10-8262-7566
E-mail: jianglei@infoc3.icas.ac.cn

[**] The authors thank the State Key Project Fundamental Research (G1999064504), the Special Research Foundation of the National Nature Science Foundation of China (29992530, 20/25/02) for continuing financial support.

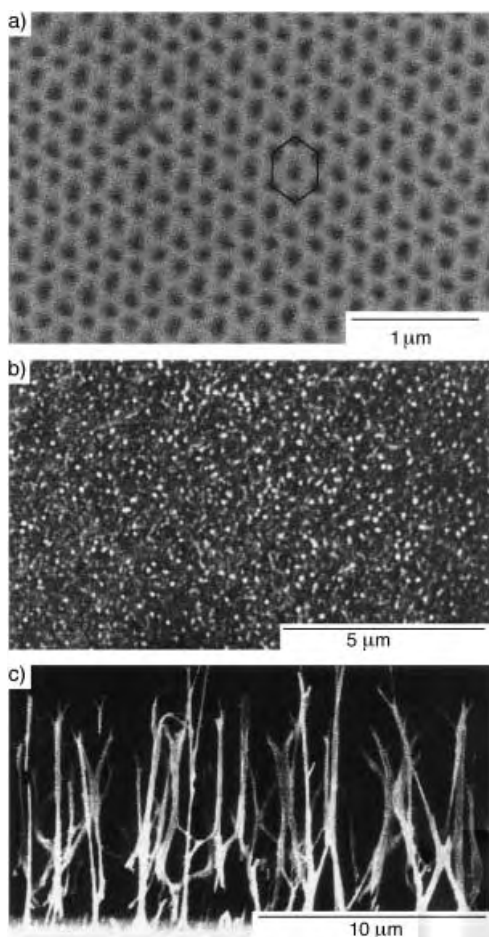


Figure 1. SEM images of a) surface of the as-prepared anodic aluminum oxide membrane; b) surface of the PAN nanofibers; c) cross-sectional view of the as-synthesized PAN nanofibers.

about 102.4 nm and a pore density of about 6.43×10^9 pores per square centimeter. Figure 1 b, a typical SEM image of the surface of PAN nanofibers, shows that aligned PAN nanofibers with end tips were obtained. The average diameter of the nanofiber tips is about 104.6 nm, which is in good agreement with the pore diameter of the template. The average interfiber distance was about 513.8 nm, and the density of the PAN nanofibers was about 2.78×10^8 fibers per square centimeter. Figure 1 c shows the cross-sectional SEM image of the as-synthesized PAN nanofibers; the length of the aligned fibers is about 10.7 μm.

Figure 1 b also shows that the surface of the PAN nanofibers is rough enough that air can be present in the troughs between individual nanofibers. Therefore, the surface of the nanofibers can be regarded as a composite surface consisting of nanofibers and air. Since surface roughness is very important to hydrophobicity,^[5, 13–15] the hydrophobicity of these PAN nanofibers was investigated. Figure 2 a shows the shape of a water droplet on the surface of our PAN nanofibers; the water contact angle is $(173.8 \pm 1.3)^\circ$. In contrast, a native PAN film with a smooth surface, prepared by coating the PAN precursor solution onto plane glass, had a water contact angle of only $(100.8 \pm 0.6)^\circ$ (Figure 2 b). That is, the PAN nanofibers with a rough surface are super-hydrophobic, while the native PAN

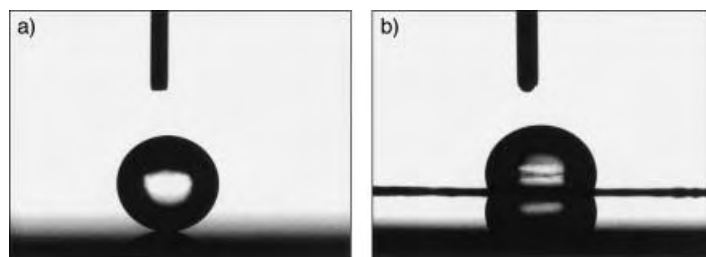


Figure 2. Shapes of water droplets on a) the PAN nanofibers with a rough surface; b) the native PAN film with smooth surface.

film with a smooth surface is merely hydrophobic. These results reveal that the nanostructure is responsible for the super-hydrophobicity. Formation of a nanostructured super-hydrophobic surface without any modification by materials of low surface free energy has not previously been reported. A possible explanation for this result is that, when nanostructured surface roughness develops, the molecules rearrange so that the number of hydrophobic groups on the surface increases. Therefore, the surface of the PAN nanofibers is super-hydrophobic but oleophilic (the contact angle for rapeseed oil is $(26.7 \pm 0.6)^\circ$). In addition, the advancing and receding angles for the PAN nanofibers are (191.2 ± 1.3) and $(136.7 \pm 0.8)^\circ$, respectively.

To thoroughly understand the hydrophobicity of the PAN nanofiber surface, theoretical considerations are necessary. The contact angle on a composite surface (θ_r) can be expressed by Equation (1).^[16] Here θ_r and θ are the contact

$$\cos \theta_r = f_1 \cos \theta - f_2 \quad (1)$$

angles on the PAN nanofibers with a rough surface and on the native PAN film with a smooth surface, respectively; f_1 and f_2 are the fractional interfacial areas of the PAN nanofibers and of the air in the troughs between individual nanofibers, respectively (i.e., $f_1 + f_2 = 1$). It is easy to deduce from this equation that increasing f_2 increases θ_r , that is, the fraction of air in the surface is important to the super-hydrophobicity.

According to Equation (1), the f_2 value of the PAN nanofiber surface is estimated to be 0.967 from the contact angles obtained from Figure 2, which indicates that the fraction of air in the surface is very high. Interestingly, the f_2 value in this case is even larger than that of the modified ACNT film (0.94).^[7] In comparison, the obvious difference is that the density of the PAN nanofibers (2.78×10^8 fibers per cm^2) is much lower than that of the ACNTs (2.43×10^{10} tubes per cm^2). Therefore, the density is also important for super-hydrophobicity. Decreasing the density (i.e., increasing the interfiber distance) should improve the water repellency. To confirm this assumption, further experiments are required.

Figure 3 shows a simple idealized model of the surface structure of the PAN nanofibers. As-

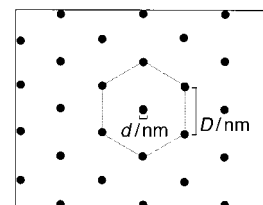


Figure 3. Model structure proposed for the surface of PAN nanofibers; d is the average tip diameter and D the average interfiber distance of the nanofibers.

suming that the nanofibers are arranged in a regular hexagonal array like the template, with an average tip diameter of d and an interfiber distance of D , the relationship of f_2 , d , and D can be described simply by Equation (2).^[17]

$$f_2 = 1 - k \left(\frac{d}{D} \right)^2 \quad (2)$$

According to this equation, f_2 is calculated to be about 0.962 from the values of d and D extracted from Figure 1 b. This f_2 value is in good accordance with that of 0.967 estimated from Equation (1), and this indicates that Equation (2) is valid. In fact, the tip diameter of the nanofibers can be regarded as a constant, because it corresponds to the pore diameter of the template. Therefore, the interfiber distance D is the essential factor that affects the f_2 value. It is easy to conclude from Equation (2) that the f_2 value will be much larger and closer to unity when D increases, that is, increasing the interfiber distance will increase the water contact angle on the nanofiber surface. This conclusion is consistent with the experimental results.

In conclusion, aligned polyacrylonitrile nanofibers were synthesized by a simple extrusion process with an anodic aluminum oxide membrane as the template. The surface of the synthesized nanofibers, without any modification by materials of low surface energy, proved to be super-hydrophobic. It is believed that not only the nanostructure of the nanofibers but also their lower density contributes to the very large fraction of air in the surface, which is essential to the super-hydrophobicity. This may provide a new method of controlling the wettability of nanostructured surfaces by changing the density of the aligned fibers.

Experimental Section

Synthesis of the PAN nanofibers: polyacrylonitrile (10.976 g, $M = 120\,000$) was dissolved in dimethylformamide (DMF, 50 mL) with stirring at 70 °C to form an 18 wt % precursor solution. A mixture of 40 wt % DMF and 60 wt % deaerated Milli-Q water was used as the solidifying solution. An as-prepared anodic aluminum oxide membrane with a pore diameter of about 102.4 nm was used as template. The PAN nanofibers were synthesized by the following process: 1) Placing a clean and dry template onto a compact polytetrafluoroethylene film and pouring the precursor onto the template. 2) Extruding the precursor into the solidifying solution under water-pump pressure (0.1 MPa). Thus, PAN nanofibers were formed in the solidifying solution. 3) Removing the solidified PAN nanofibers and washing the completely solidified surface with deionized water several times and then drying in air. 4) Collecting the used template and washing it with deionized water and acetone in turn several times, after which the template can be recycled.

SEM images were obtained with a Hitachi S-530 scanning electron microscope at 25 kV. Contact angles were measured on a dataphysics OCA20 contact-angle system at ambient temperature. Water droplets (about 3.8 μ L) were dropped carefully onto the PAN nanofiber surface and on the native PAN film. The average contact angle value was obtained by measuring at five different positions of the same sample.

Received: September 18, 2001

Revised: December 28, 2001 [Z17929]

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- [17] If each hexagon composed of seven nanofibers is a unit, then f_2 can be regarded as being equal to the open area and expressed as follows:

$$f_2 = \frac{3(D \sin 60^\circ) - 3\pi \left(\frac{d}{2} \right)^2}{3(D \sin 60^\circ) - 1 - \frac{\pi}{2\sqrt{3}} \left(\frac{d}{D} \right)^2} = 1 - k \left(\frac{d}{D} \right)^2$$

$$k = \text{const.} = \frac{\pi}{2\sqrt{3}}$$

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A Reactive Intermediate in the Synthesis of Iron Arsenates: Synthesis of the First One-Dimensional Iron Arsenate Oxalate and Its Transformation into Two- and Three-Dimensional Iron Arsenates**

Sandip Chakrabarti and Srinivasan Natarajan*

Phosphate-based networks exhibiting open architectures have been prepared and studied with great intensity during the last two decades.^[1] While it is desirable to synthesize large number of materials with new architectures, it is also important to understand the role of the building units and the reaction pathways involved in the formation of these solids.^[2, 3] To this end, the principle of building up three-dimensional (3D) structures from structures of lower dimensionalities may be useful.^[4] The transformation of a one-dimensional (1D) gallium phosphate into a 3D structure, under real time conditions, is a good example of this principle.^[5, 6] The scope of the building up process has not been investigated in detail because of the lack of reactive lower (one-)dimensional solids. Recently, there has been growing interest in the study of arsenate-containing phases and the interplay of the chemical and geometric factors in determining their framework topology and composition.^[7] We have been concerned with understanding the formation of framework solids and are investigating the transformation of lower-dimensional zinc phosphates, which has resulted in better understanding of the pathways involved in the formation of these phases.^[4, 8, 9] During this study, we prepared an iron arsenate oxalate, $[\text{C}_4\text{N}_2\text{H}_{12}][\text{Fe}(\text{OH})(\text{HAsO}_4)(\text{C}_2\text{O}_4)] \cdot \text{H}_2\text{O}$ (**I**), with a 1D edge-shared ladder structure and pendant oxalate groups on the iron centers, by use of hydrothermal methods. To our knowledge, this is the first iron arsenate oxalate material to be synthesized in the presence of an organic amine. Remarkably, **I** may be transformed into a two-dimensional (2D) iron arsenate, $[\text{C}_4\text{N}_2\text{H}_{12}]_{1.5}[\text{Fe}_3\text{F}_5(\text{AsO}_4)(\text{HAsO}_4)_2]$ (**II**), and a mixed-valent 3D iron arsenate, $[\text{C}_4\text{N}_2\text{H}_{12}][\text{Fe}^{\text{III}}\text{Fe}^{\text{II}}(\text{AsO}_4)_2(\text{HAsO}_4)_2]$ (**III**). This observation not only shows the importance of the building up process, but also establishes the reactive nature of lower-dimensional solids. It is of note that while **I** and **II** contain iron centers in +3 oxidation state, in **III**, the iron centers are in +2 and +3 oxidation states.

The structure of **I** comprises strictly alternating FeO_6 and AsO_4 polyhedral units, which form an edge-shared 1D ladder structure with the oxalate units pendant from the Fe centers (Figure 1 a). A doubly protonated piperazine molecule occupies the inter-ladder space and interacts with the framework

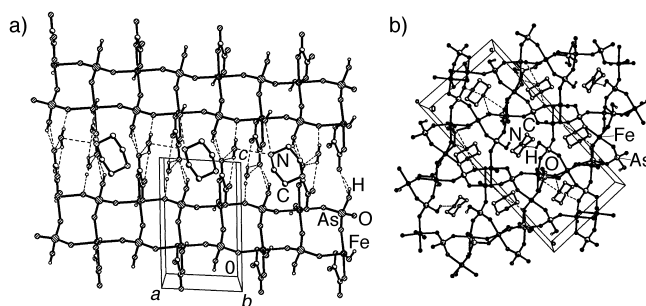


Figure 1. a) Structure of **I** in the *ac* plane, showing the ladder arrangement and the oxalate group pendant from the Fe center. Dotted lines represent hydrogen bonds. b) Structure of **II** in the *bc* plane, showing a single layer. The zigzag Fe-F chains are linked by SBU-4.

through hydrogen bonds. The structure of **I** is isotypic with the recently described vanadyl phosphate oxalate, $[\text{C}_4\text{N}_2\text{H}_{12}][\text{VO}(\text{HPO}_4)(\text{C}_2\text{O}_4)]$.^[10] The oxalate units in **I** occupy a similar position to that of the pendant phosphates in the 1D ladder structures.^[4, 9] This observation prompted us to investigate the transformation of **I** under various conditions, as ladder zinc phosphates have been shown to undergo facile transformation into higher dimensional structures,^[9a] though such studies have not been undertaken in any other system of compounds. Thus, **II** and **III** were obtained as good-quality single crystals by the prolonged reaction of **I**.

The structure of **II** is similar to the iron–arsenate structure reported recently by Luo et al.,^[11] which consists of infinite chains of corner-sharing FeX_6 ($\text{X} = \text{O}, \text{F}$) octahedra and dimers of edge-sharing FeO_3F_3 octahedra, linked into 2D sheets through arsenate tetrahedra (Figure 1 b). The piperazinium cations occupy interlamellar space and interact with the framework through $\text{N}-\text{H} \cdots \text{O}$ hydrogen bonds. Strong interlayer hydrogen bonds between the terminal OH groups of HAsO_4 lead to the formation of pseudo-1D channels. The edge-shared dimer with the arsenate group has been classified as an SBU-4 (secondary building unit) and has been observed in many ULM-*n* phases.^[2]

Unlike **II**, compound **III** does not have any fluorine atoms in its framework. The fluorine atoms are replaced by three-coordinate oxygen atoms. The structure consists of a network of FeO_6 octahedra and AsO_4 tetrahedra, linked through their vertices to form a unique 3D structure. The framework structure can be understood in terms of secondary building units. Thus, four three-coordinate oxygen atoms connect three iron atoms, which form an Fe_3O_{14} core consisting of two Fe^{III} atoms and an Fe^{II} atom, all of which are perfectly ordered, as shown in Figure 2 a. This is the first time, to our knowledge, that this trimer unit has been observed in an iron–arsenate system. The Fe_3O_{14} trimeric core is connected to HAsO_4 tetrahedra in an out-of-plane mode, through the three-coordinated oxygen atoms (Figure 2 b), which forms four interconnected SBU-4 units. These SBU-4 units are further linked by AsO_4 tetrahedra, to form an unusual $[\text{Fe}_6\text{As}_8\text{O}_{36}(\text{OH})_4]$ cluster, which is connected through the oxygen atoms, which results in large 1D tunnels surrounded by 12 T atoms ($\text{T} = \text{As}$) along the [001] direction as shown in Figure 3. The AsO_4 units cover all the tunnel walls. This may be contrasted with the open-framework nickel phosphate

[*] Prof. Dr. S. Natarajan, S. Chakrabarti
Framework Solids Laboratory
Chemistry and Physics of Materials Unit
Jawaharlal Nehru Centre for Advanced Scientific Research
Jakkur P.O., Bangalore 560 064 (India)
Fax: (+91) 80-846-2766
E-mail: raj@jncasr.ac.in

[**] The authors thank Prof. Dr. C. N. R. Rao, FRS for his kind help, support, and encouragement. S.N. thanks the Department of Science and Technology (DST), Government of India, for a research grant.

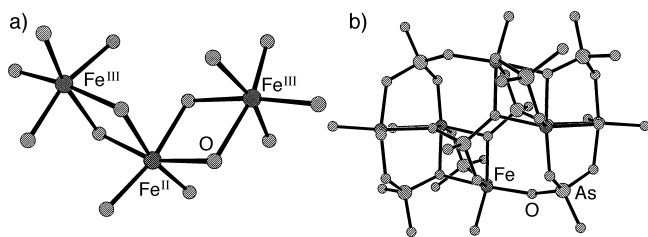


Figure 2. a) The unusual building unit observed in **III**, the Fe–O trimer, $[\text{Fe}_3\text{O}_{14}]$. Note the ordering of the Fe^{III} and Fe^{II} centers. b) The $[\text{Fe}_6\text{As}_8\text{O}_{36}(\text{OH})_4]$ cluster in **III**. Note the presence of SBU-4 units and their connectivity.

structure described recently, in which the tunnel walls consist only of NiO_6 octahedra.^[12] The structure of **III**, constructed entirely of SBU-4 units, can be considered as the upper homologue of ULM-4.^[2] The various structural features in **III** have been observed for the first time.

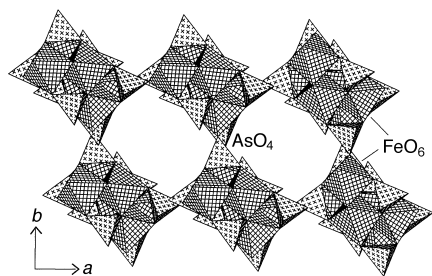


Figure 3. Structure of **III** in the bc plane showing the large 1D tunnels. The tunnel walls consist only of the arsenate tetrahedra. The amine molecules are not shown.

The bond distances and angles in **I–III** are in the ranges expected for this type of bonding. The observed average As–O distance is 1.6954 Å, the O–As–O bond angle is 109.5°, the Fe–O/F distance is 2.0051 Å, and the O/F–Fe–O/F angle is 106°, all of which are in agreement with those values reported in the literature.

An examination of the structures of **I**, **II**, and **III** reveals the similarities between them. Compounds **II** and **III** possess the same building unit (SBU-4) formed with fluorine and oxygen atoms, respectively, but linked differently. In contrast, **I** contains only four-membered rings. The formation of SBUs from **I**, however, can be easily visualized, as it possesses a terminal oxalate group. Metal oxalates have traditionally been employed as the initial reactive source of metal ions, in the synthesis of open-framework materials. It is possible that, during the hydrothermal reaction, the oxalate group leaves the framework, and the F^- ion attacks the bare iron atom and links two iron atoms within the ladder, which forms Fe–F–Fe 1D chains, such as those observed in **II** (Figure 1b). The continuous reaction of F^- ions at the Fe center may also lead to a breakdown of the ladder, thereby causing formation of four-membered rings and the linking of pairs of iron centers by two F^- ions. This breakdown of the ladder would result in SBU-4. These building units are connected through the arsenate units forming the structure of **II**. In the case of **III**,

we find that two four-membered rings form the SBU-4 units, and are joined through three-coordinate oxygen to form a $[\text{Fe}_3\text{O}_{14}]$ trimer, which is then connected through arsenate tetrahedra to form the framework. The formation of four-membered rings appears in both cases to be crucial, as such four-membered-ring monomers have been isolated and shown to be highly reactive in the formation of 1D, 2D, and 3D structures.^[8, 9a] This hypothesis suggests that the transformation of the ladder material to the 3D structure is a solution-mediated process, which involves dissolution of the first phase, rather than a solid-state transformation. A schematic of the formation, from **I**, of the various building units observed in **II** and **III** is shown in Figure 4. A key feature

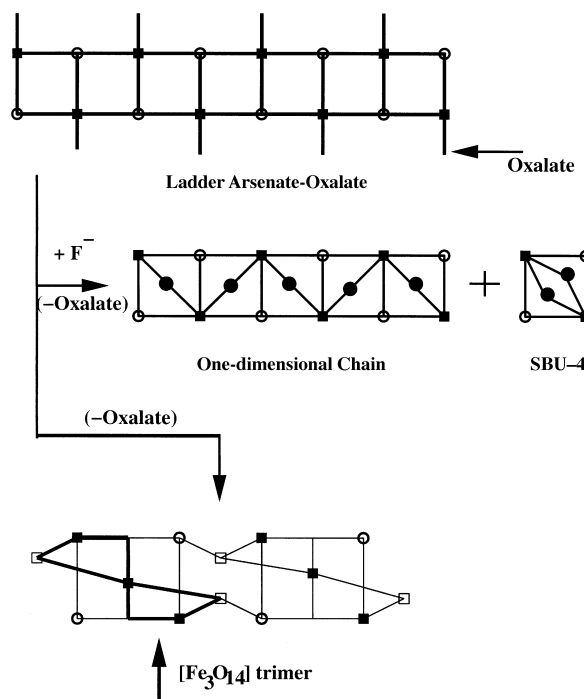


Figure 4. A schematic of the formation of the secondary-building units (SBU) observed in **II** and **III**. ■ Fe, ○ As, ● F, □ O (three coordinate).

in this evolution is the existence of the same tetramers (SBU-4) which act as building blocks in the solids. It is likely that the reaction pathway (Figure 4) can be followed by in situ synchrotron radiation experiments, as such studies have been used to elucidate similar building processes.^[5, 6, 13, 14] Within this hypothesis, the identification by Taulelle et al. of various oligomeric building blocks, under hydrothermal reaction conditions and by using NMR spectroscopy, is also important.^[15]

In summary, a 1D ladder iron arsenate oxalate has been prepared for the first time, and shown to be reactive. This is the first time that the transformation of a low-dimensional solid has been observed in a family of transition metal arsenates and arsenate oxalates. It is likely that crystalline materials with unknown structures might also be formed during the hydrothermal reactions. The sequential crystallization of 2D (**II**) and 3D (**III**) structures from **I** shows the evolution of a chemical system.

Experimental Section

Colorless rodlike crystals of **I** were obtained in ~40% yield, by the hydrothermal reaction in the presence of piperazine (PIP). Typically, a mixture of $\text{Fe}(\text{C}_2\text{O}_4) \cdot 2\text{H}_2\text{O} \cdot \text{H}_3\text{AsO}_4 \cdot \text{PIP} \cdot \text{HF} \cdot \text{water}$ (1:8:4:6:200) was heated at 150 °C for 72 h in a PTFE-lined acid digestion bomb (7 mL). The initial pH of the reaction mixture was 2; this did not change significantly after the heat treatment. Mildly pink colored platelike crystals of **II** (50% yield) were obtained by reacting the above mixture at 150 °C for 168 h or at 180 °C for 24 h, and deep green colored rodlike crystals of **III** (35% yield) resulted when the mixture was heated at 180 °C for 60 h. **II** and **III** can also be obtained by heating a mixture of $\text{Fe}(\text{acac})_3 \cdot 6\text{H}_3\text{AsO}_4 \cdot 4\text{PIP} \cdot 4\text{HF} \cdot 200\text{H}_2\text{O}$ at 180 °C for 48 h, or $\text{Fe}(\text{C}_2\text{O}_4) \cdot 2\text{H}_2\text{O} \cdot 8.6\text{H}_3\text{AsO}_4 \cdot 1.4\text{PIP} \cdot 285\text{H}_2\text{O}$ at 150 °C for 48 h. When the crystals of **I** (0.5 g) were heated with water (2 mL) at 150 °C in an acid digestion bomb, **III** was formed, along with a mixture of condensed iron arsenates. The compounds **I**, **II**, and **III** have been obtained as pure single-phase materials, and were characterized using energy dispersive X-ray analysis (EDAX), IR, and thermogravimetric analysis (TGA). An X-ray photoemission spectroscopy (XPS) investigation clearly indicated the presence of both Fe^{II} and Fe^{III} species in **III**.

Suitable single crystals of **I**, **II**, and **III** were subjected to X-ray diffraction studies on a Siemens SMART-CCD diffractometer at 298 K. Crystal data for **I**: triclinic, space group $P\bar{1}$ (no. 2), $a = 6.5668(3)$, $b = 9.1040(3)$, $c = 10.4715(4)$ Å, $\alpha = 86.35(1)^\circ$, $\beta = 85.34(1)^\circ$, $\gamma = 83.32(4)^\circ$; $V = 618.8(1)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.184$ g cm⁻³, and $\mu(\text{MoK}\alpha) = 3.928$ mm⁻¹. Crystal data for **II**: monoclinic, space group $P2_1/c$ (no. 14), $a = 8.4048(1)$, $b = 22.000(5)$, $c = 10.848(2)$ Å, $\beta = 95.97(1)^\circ$; $V = 1995.0(7)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.709$ g cm⁻³, and $\mu(\text{MoK}\alpha) = 7.201$ mm⁻¹. Crystal data for **III**: monoclinic, space group $C2/c$ (no. 15), $a = 14.6850(3)$, $b = 10.6696(3)$, $c = 10.1699(3)$ Å, $\beta = 90.12(1)^\circ$; $V = 1593.4(1)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 3.067$ g cm⁻³, and $\mu(\text{MoK}\alpha) = 9.993$ mm⁻¹. For **I**, a total of 2632 reflections were collected and merged to give 1754 unique reflections ($R_{\text{int}} = 0.02$) of which 1488 with $I > 2\sigma(I)$ were observed. For **II**, a total of 8348 reflections were collected and merged to give 2867 unique reflections ($R_{\text{int}} = 0.06$) of which 2393 with $I > 2\sigma(I)$ were observed. For **III**, a total of 3255 reflections were collected and merged to give 1145 unique reflections ($R_{\text{int}} = 0.04$) of which 993 with $I > 2\sigma(I)$ were observed. The structures were solved and refined using the SHELXTL-PLUS programs to obtain $R_1 = 0.04$, $wR_2 = 0.1$, and $S = 1.06$ for 190 parameters for **I**, $R_1 = 0.04$, $wR_2 = 0.09$, and $S = 1.07$ for 289 parameters for **II**, $R_1 = 0.03$, $wR_2 = 0.08$, and $S = 1.03$ for 121 parameters for **III**. The piperazine molecules within the channels in **III** were difficult to locate, and only a fragment of the molecule was observed. It is likely that the piperazine molecule decomposed during the preparation of the crystal. CCDC-172356 (**I**), -172357 (**II**), and -172358 (**III**) 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 (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).

Received: October 23, 2001
Revised: January 17, 2002 [Z18105]

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[Zn₄(thf)₄(MeZn)₄(O₃SiR)₄] (R = 2,6-*i*Pr₂C₆H₃N(SiMe₃)), A Compound Containing Trigonal-Planar, Tetrahedral, and Trigonal-Bipyramidal Metal Atoms: A New Route to Larger Aggregates**

Ganapathi Anantharaman, Herbert W. Roesky,* and Jörg Magull

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

Metallasiloxanes derived from Si-OH species have received considerable attention in recent years. A number of such compounds obtained starting from monosilanol, silanediol, silanetriol, disilanol, and trisilanol have been discussed in recent reviews.^[1] These compounds can be used as precursors for metal silicates and mixed-metal oxide systems^[2] as well as for models for heterogeneous silica-supported catalytic systems.^[3] Recently, a zinc-containing zeolite (H-ZSM5) system has been reported that catalyzes aromatization reactions, dehydrochlorination and dehydrofluorination, and conversion of methyl iodide to hydrocarbons.^[4] Metallasiloxanes are also important because of their ability to act as model compounds for complex zeolite systems.^[5] In recent years we have synthesized a variety of metallasiloxane compounds starting from kinetically stable silanetriol (2,6-*i*Pr₂C₆H₃N(SiMe₃)Si(OH)₃) that exhibits novel structural features.^[6] We^[7] and others^[8] have also reported that the framework of aluminosiloxane and gallasiloxane compounds has similar structural features to naturally occurring mineral and zeolite systems.

A polyhedral zinc siloxane compound which was obtained by using dimethylzinc and trimethylsilanol has been reported by Schmidbaur et al.^[9] More recently, dimeric, trimeric, and

[*] H. W. Roesky, G. Anantharaman, J. Magull
Institut für Anorganische Chemie
Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)
Fax: (+49) 551-393373
E-mail: hroesky@gwdg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Göttinger Akademie der Wissenschaften.

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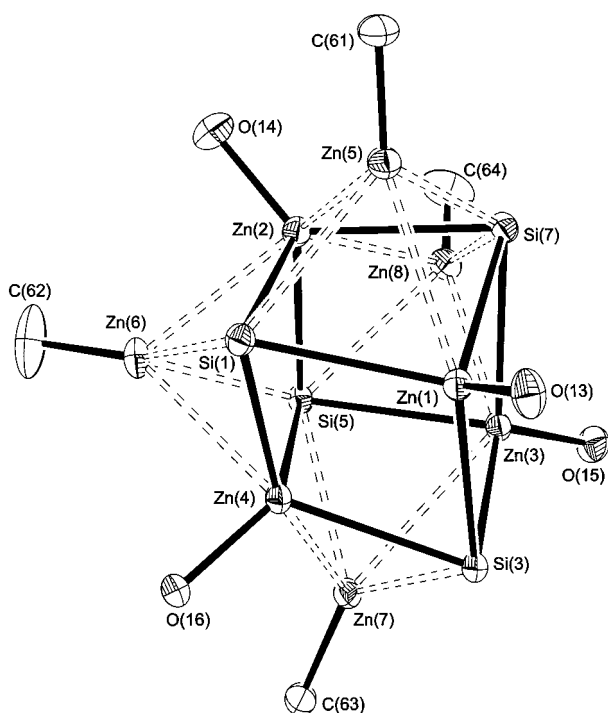


Figure 2. The arrangement of zinc and silicon atoms in the molecular structure of **2**. Imaginary lines are drawn between zinc and silicon atoms. Carbon, hydrogen, nitrogen, and oxygen atoms have been omitted for clarity (except for a few carbon and oxygen atoms around zinc).

Zn(7) 2.950(1) Å) indicates a weak M–M interaction.^[15] Similarly, the average Zn...Si distance is 2.748(1) Å, and we suggest that there may be an interaction between these atoms given that the Zn–Si single bond length in [Zn{Si(SiMe₃)₃}₂] is 2.342 Å.^[16] The average Zn–C and Si–O bond lengths (1.948(4) and 1.635(3) Å, respectively) lie in the expected range.^[9, 10] In addition, there are two unusually long Zn–O bond lengths observed for the two tetrahedral zinc atoms (Zn(7)–O(6) 2.317(3), Zn(8)–O(10) 2.352(3) Å) and the remaining Zn–O bond lengths fall in the range of 1.911(3)–2.203(3) Å.

In summary, by changing the reaction conditions we were able to obtain a larger aggregate of oligonuclear zinc siloxane **2**, which exhibits a novel structural feature namely, zinc atoms in a variety of geometries and coordination environments and a chelating and bridging mode of the siloxane moiety. Furthermore, the hydrolyzable functionalities in compound **2** make it a potential precursor for the preparation of new synthetic Zn-containing zeolites under mild conditions or by sol–gel procedures.

Experimental Section

2: A solution of Me₂Zn (4 mL of a 2 M solution in toluene, 8.00 mmol) was slowly added to a suspension of RSi(OH)₃ (1.07 g, 3.87 mmol) in THF/hexane (5 mL, 40 mL) at room temperature. After the evolution of methane gas ceased, the resulting solution was further stirred for 16 h at room temperature. The volatile components were removed and the residue was dried for 6 h under vacuum. The remaining solid was washed with THF/hexane (1/1) and finally recrystallized from toluene (5 mL) to yield colorless crystals of **2** at 0 °C (1.2 g, 64%). M.p. > 200 °C; ¹H NMR (500 MHz, C₆D₆): δ = −0.1, 0.018, 0.037, 0.060, 0.093 (s, 12H; ZnMe), 0.39 (m, 36H; SiMe₃), 0.37 (m, 48H; CH(CH₃)₂), 1.55 (m, 16H; OCH₂CH₂),

3.70 (m, 16H; OCH₂), 3.81 (br, 8H; CH(CH₃)₂), 7.01 (m, 12H; arom.); ²⁹Si NMR (99.36 MHz, C₆D₆): δ = 3.58, 4.10 (s; Si(CH₃)₃), −60.87, −61.34 (br; SiO₃).

Received: November 5, 2001 [Z18158]

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- Crystal data for compound **2**·3C₇H₈: C₁₀₁H₁₇₂N₄O₁₆Si₈Zn₈, *M*_r = 2446.11, triclinic, space group *P* $\bar{1}$, *a* = 14.5274(7), *b* = 16.0523(10), *c* = 27.4893(14) Å, α = 99.197(4), β = 91.338(4), γ = 112.005(4)°, *V* = 5842.7(5) Å³, *Z* = 2, ρ_{calcd} = 1.390 mg m^{−3}, *F*(000) = 2572, λ = 0.71073 Å, *T* = 133(2) K, μ (MoK α) = 0.904 mm^{−1}. Crystal size 0.2 × 0.3 × 0.3 mm. The data were collected by using the ω scan mode in the range of 1.52 ≤ θ ≤ 24.82, −17 ≤ *h* ≤ 17, −18 ≤ *k* ≤ 18, −32 ≤ *l* ≤ 32. Of 39 805 reflections collected, 17 747 were unique. Final *R*1 [*I* > 2 σ (*I*)] = 0.0393; *wR*2 (all data) = 0.0961. Maximum and minimum heights in the final Fourier difference map were 0.877 and −0.653 e Å^{−3}. The single crystals suitable for X-ray diffraction studies

of compound **2** ($\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$) were obtained from toluene at 0°C . Diffraction data were collected on a IPDS II Stoe image-plate diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct methods (SHELX-97)^[17] and refined against F^2 on all data by full-matrix least-squares with SHELX-97.^[18] The heavy atoms were refined anisotropically. Hydrogen atoms were included by using the riding model with U_{iso} tied to U_{iso} of the parent atoms. CCDC-173318 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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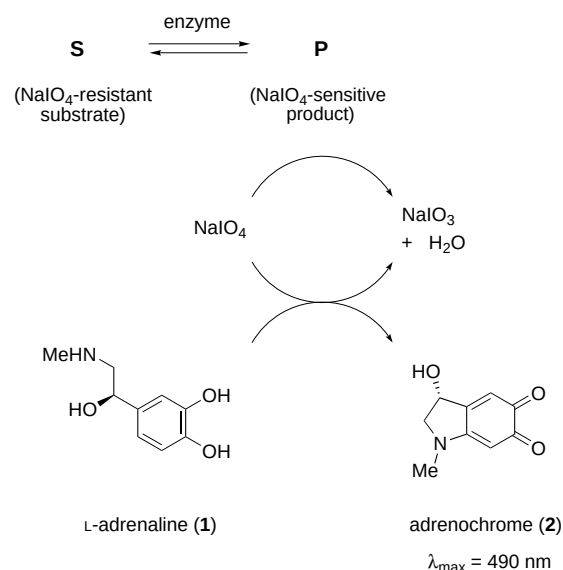
The Adrenaline Test for Enzymes**

Denis Wahler and Jean-Louis Reymond*

Enzyme assays^[1] play a key role in the search for novel enzymes,^[2] which are in great demand as components of consumer products, industrial processes, diagnostics, and analytical reagents.^[3] While many enzyme assays are based on chromogenic or fluorogenic substrates, it is often desirable to have assays that produce a recordable signal indirectly and thus avoid the incorporation of a chromophore into the substrate itself. Such indirect assays are possible with sensors that either record changes in physicochemical parameters such as temperature,^[4] pH,^[5] or $\text{pM}^{[6]}$ upon reaction progress, or that respond by selective recognition of product over substrate through noncovalent interactions.^[7, 8] The classical enzyme-coupled enzyme assays achieve the same goal through selective degradation of the reaction product by

one or more secondary enzymes, most often by means of a redox chain that leads to the formation of NADH, which is analyzed spectrophotometrically at 340 nm .^[9] Enzyme-coupled assays are, however, expensive and incompatible with varying technically important parameters such as cosolvents, pH, and temperature. Herein we report a colorimetric enzyme assay based on the quantification of periodate-sensitive reaction products by back-titration of the oxidant with adrenaline. The assay uses inexpensive, commercially available reagents, and offers a simple solution for assaying a variety of industrially important enzymes with their natural substrates.

We recently reported a series of enzyme substrates that released a colored or fluorescent product by oxidation of the primary enzyme reaction product by alcohol dehydrogenase^[10] or sodium periodate.^[11] Considering that sodium periodate reacts rapidly with any 1,2-diol or related periodate-sensitive functional groups independent of the presence of a chromophore in the molecule, we reasoned that this oxidant should also be applicable to nonchromogenic and nonfluorogenic substrates if used in a back-titration mode. Thus, any periodate-sensitive reaction product formed from a periodate-resistant substrate should be detectable by adding first a measured amount of sodium periodate, and second a chromogenic or fluorogenic reagent to quantitate the unreacted sodium periodate by optical density (OD) measurements (Scheme 1).



Scheme 1. Principle of the adrenaline test for enzymes.

Adrenaline (**1**) reacts within seconds with sodium periodate to form the red dye adrenochrome (**2**).^[12] We have found that this reaction can be used to quantitate sodium periodate independent of the presence of proteins or cosolvents at any pH between 2 and 10 in aqueous buffers.^[13] The reaction enabled us to measure various periodate-sensitive functional groups such as 1,2-diols, 1,2-aminoalcohols, 1,2-diamines and α -hydroxyketones by back-titration of sodium periodate (Figure 1).

[*] Prof. Dr. J.-L. Reymond, Dr. D. Wahler
Department of Chemistry & Biochemistry
University of Bern
Freiestrasse 3, 3012 Bern (Switzerland)
Fax: (+41) 31-631-8057
E-mail: jean-louis.reymond@ioc.unibe.ch

[**] We would like to thank Prof. R. Furstoss and Dr. A. Archelas at the Faculté des Sciences de Luminy, Marseille, France, for providing a sample of *Aspergillus niger* EH and Dr. C. Weijers at the Department of Food Technology and Nutrition Sciences, Wageningen University, the Netherlands, for providing a sample of *Rhodotorula glutinis* EH. This work was supported by the University of Bern, the Swiss National Science Foundation, and Protéus SA (Nîmes, France).

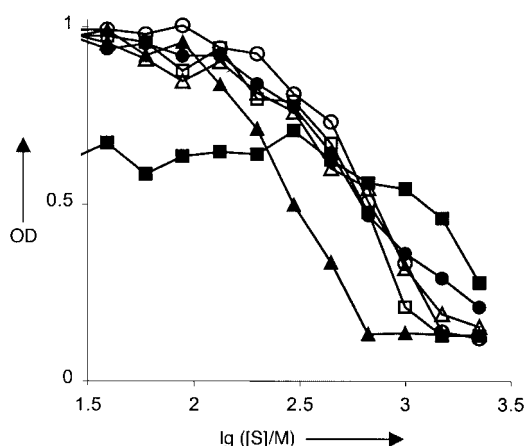
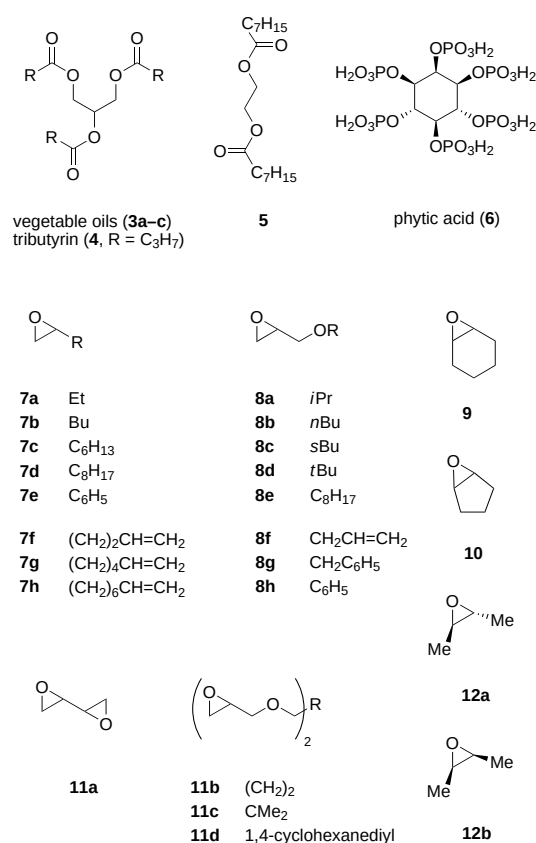


Figure 1. Detection of diols, aminoalcohols, diamines, and hydroxyketones by back-titration of sodium periodate with adrenaline. Observed OD at 490 nm (as given by microtiter-plate reader) is shown as a function of the molar concentration of diol or aminoalcohol (S; substrate) in logarithmic scale, as recorded after oxidation with NaIO_4 (1 mM) for 30 min, followed by reaction with **1** (1.5 mM) for 5 min in 20 mM aq phosphate pH 7.2, 26 °C. (●) inositol (EC_{50} = 0.65 mM), (○) benzoine (EC_{50} = 0.71 mM), (▲) glycerol (EC_{50} = 0.31 mM), (□) ethanolamine (EC_{50} = 0.66 mM), (△) ethylene glycol (EC_{50} = 0.76 mM), (■) ethylene diamine in 20 mM aqueous borate at pH 8.8 (EC_{50} = 1.38 mM). EC_{50} is the concentration that inhibits 50 % of the color reaction.

The assay was first applied to measure the activity of lipases and esterases (Figure 3). The back-titration readily detected the interfacial lipolytic activities of the enzymes under biphasic conditions with various vegetable oils (**3a–c**, Scheme 2), which release glycerol upon hydrolysis, as substrates. Interestingly, the pH-indicator method^[5] failed to give any signal for these substrates, probably because the products, long-chain fatty acids, remain in the oil phase. The assay was also suitable for detecting esterolytic activities with soluble aliphatic esters such as tributyrin (**4**) and ethylene glycol bisoctanoate (**5**, Figure 2).

We next turned our attention to phytases, a class of acid phosphatases that hydrolyze phytic acid (**6**, Scheme 2) to less phosphorylated *myo*-inositol derivatives. Phytases are used industrially to increase the nutritional value of animal feed.^[14] The back-titration with adrenaline could be expected to respond to the hydrolysis of at least two vicinal phosphate groups on phytic acid, which corresponds to the dephosphorylation pattern of most phytases.^[14b, 15] The assay was used to record the pH profile of the phytases^[16] by taking advantage of the pH-independent formation of adrenochrome (Figure 3). The assay offers a useful alternative to the colorimetric titration of inorganic phosphate for screening phytases with their natural substrate.^[17]

The versatility of our assay in terms of substrate structures was demonstrated for epoxide hydrolases, which produce 1,2-diols from epoxides.^[18] Twenty-four commercially available aliphatic and aromatic epoxides (**7–12**, Scheme 2) were assayed with epoxide hydrolases from *Aspergillus niger*^[19] and *Rhodotorula glutinis*.^[20] The reactivity pattern for the substrate series was recorded with both enzymes under their optimal operating conditions (Figure 4). This is the first generally applicable chromogenic assay for epoxide hydrolases.^[21]



Scheme 2. Structures of enzyme substrates used in this study.

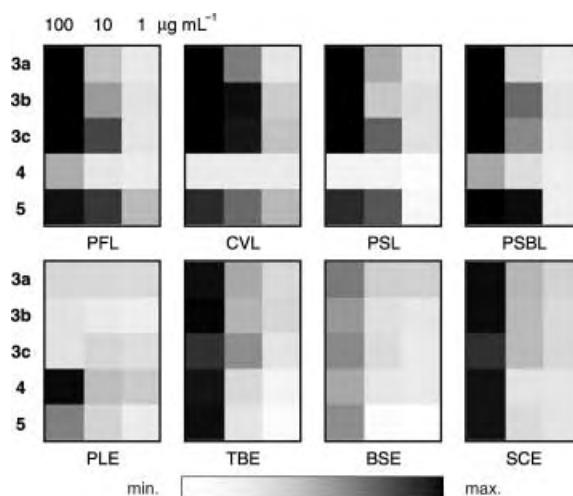


Figure 2. Activity of lipases (upper row of blocks) and esterases (lower row) on vegetable oils (**3a** = olive oil, **3b** = sunflower oil, **3c** = grapeseed oil), tributyrin (**4**), and ethylene glycol bisoctanoate (**5**) as determined by the adrenaline test. For each enzyme (3 × 5 grid), each grayscale square shows the percent reduction of OD_{490} from white (0 %, no activity) to black (100 %, maximum activity) for the indicated substrate (row) at the indicated enzyme concentration (column). Conditions: 1) enzyme in 20 mM aq. phosphate pH 7.2, 1 mM NaIO_4 , vegetable oils **3a–c** (0.05 mL, 0.4-mL assay in 1.5-mL Eppendorf tube, shaker at 1200 rpm) or soluble substrate **4** and **5** (10 mM), 26 °C, 30 min.; 2) 1.5 mM **1**, 5 min. Key for enzyme samples (Fluka ref.): PFL = *Pseudomonas fluorescens* lipase (F62321); CVL = *Chromobacterium viscosum* lipoprotein lipase (F62333); PSL = *Pseudomonas* sp. lipoprotein lipase (F62335); PSBL = *Pseudomonas* sp. Type B lipoprotein lipase (F62336); PLE = pig liver esterase (F46058); TBE = *Thermoanaerobium Brockii* esterase (F46061); BSE = *Bacillus* sp. esterase (F46062); SCE = *Saccharomyces cerevisiae* esterase (F46071).

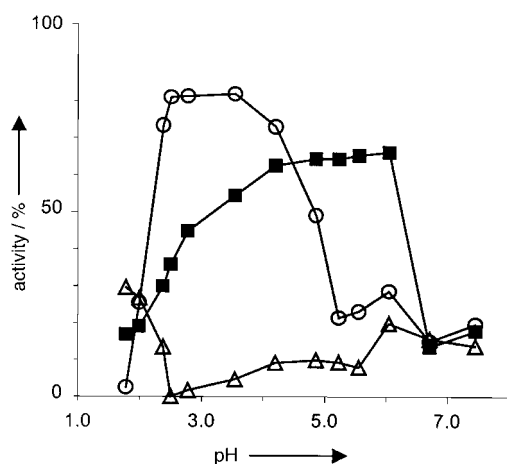


Figure 3. pH Profile of phytases recorded by the adrenaline test. Activity is reported as the percent reduction of OD₄₉₀ relative to reference. Conditions: 1) 10 mM aq potassium phytate (6) with 1 mM CaCl₂ at the indicated pH, phytase (0.1 mg mL⁻¹), 60 min at 55°C; 2) 1 mM NaIO₄, 30 min, 26°C; 3) 1.5 mM **1**, 5 min (■) Natuphos® phytase, (△) Novo phytase, (○) *Aspergillus ficuum* phytase. There was no detectable activity in the controls without enzyme.

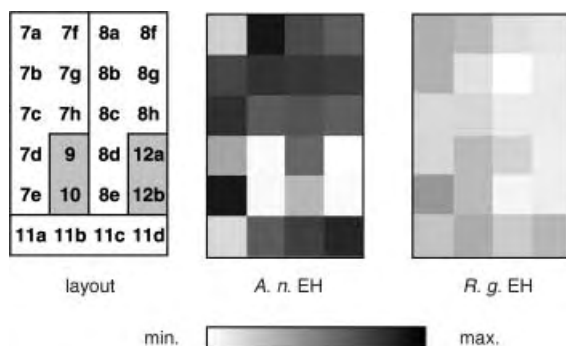


Figure 4. Hydrolytic activities of epoxide hydrolases (EH) towards epoxides 7–12 as measured by the adrenaline test. Each grayscale square corresponds to one epoxide according to the layout at left, and shows the percent reduction of OD₄₉₀ from white (0%, no activity) to black (100%, maximum activity). Left: *Aspergillus niger* EH (0.05 mg mL⁻¹, partially purified enzyme preparation), 26°C. Right: *Rhodotorula glutinis* EH (0.1 mg mL⁻¹, crude enzyme extract), 37°C. Conditions: 1) 10 mM epoxide in aq. 20 mM phosphate pH 7.2, enzyme, 1 mM NaIO₄, 30 min at the indicated temperature; 2) 1.5 mM **1**, 5 min, 26°C. There was no detectable hydrolysis in control assays without enzyme or with BSA (bovine serum albumin, 2 mg mL⁻¹).

The examples above demonstrate the high-throughput potential and versatility of the adrenaline test for enzymes. The assay quantitates vicinal diols, aminoalcohols, diamines, and α -hydroxyketones (Figure 1), and can be used generally to assay reactions of such functional groups as substrates or as products. As is the case for many catalysis assays such as cat-ELISA (catalytic enzyme-linked immunoabsorbent assay),^[8a] and screening methods based on TLC (thin-layer chromatography),^[22] MS (mass spectrometry),^[23] or capillary electrophoresis CE,^[24] the periodate back-titration is only suited for endpoint measurements. Nevertheless, the method is close to ideal since it combines a broad versatility in terms of substrate structure, reaction types, and reaction conditions, with a single, commercially available and inexpensive chromogenic

probe that produces a signal directly visible by the eye. This assay is also suited for miniaturization in ultrahigh-throughput screening format.

Experimental Section

Substrates were diluted from 10 mM stock solutions in acetonitrile. Vegetable oils were used pure. Enzymes were diluted from 1 mg mL⁻¹ stock solutions in phosphate-buffered saline (160 mM NaCl, 10 mM aq. phosphate, pH 7.4). NaIO₄ was added as a freshly prepared 10 mM stock solution in water. Adrenaline (as the HCl salt) was added as a 10 mM stock solution in water. Assays (0.1 mL) were conducted in individual wells of 96-well flat-bottom half-area polystyrene microtiter plates (Costar) as described in the figure legends. The optical density was recorded with a Spectramax 250 Microplate Spectrophotometer (Molecular Devices, λ = 490 nm).

Received: October 31, 2001

Revised: January 7, 2002 [Z18137]

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- Sodium periodate can also be quantitated with other catechols, including 3-methoxycatechol (λ_{max} = 405 nm for the quinone) and 2,3-

dihydroxynaphthalene or 3,4-dihydroxybenzoate (extinction of blue fluorescence at $\lambda_{\text{em}} = 440$ nm upon oxidation to the quinone). Noradrenaline reacts similarly to adrenaline down to pH 5. Adrenochrome (**2**) is unstable and polymerizes to brown and finally insoluble black products upon prolonged standing in solution.

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Cubane with a Handle: $[\{\text{In}_3\text{As}_4\text{Nb}\}-\text{As}]^{7-}$ in $\text{Cs}_7\text{NbIn}_3\text{As}_5$ **

Franck Gascoin and Slavi C. Sevov*

Compared to the large number of main group Zintl compounds there are only a few that contain transition metals.^[1] This is not surprising since the traditional definition of Zintl phases automatically excludes transition metals. However, many such compounds with transition metals can

qualify for Zintl phases when a broader definition is used. The latter includes compounds of transition metals with filled or empty d shells, that is the late transition metals of the Ni, Cu, and Zn groups,^[2] and the early transition elements of the Ti, V, and Cr groups at maximum formal oxidation states.^[3] There are only two Zintl compounds containing a transition metal with partially filled d shell, both based on manganese, $(\text{AE})_{14}\text{MnPn}_{11}$ (AE = alkaline-earth metal, Pn = pnictogen) and $\text{Sr}_{21}\text{Mn}_4\text{Sb}_{18}$.^[4] Perhaps only they should be called true “transition metal Zintl phases” although the name is contradictory in itself. All but two of the d^0 compounds contain isolated tetrahedra $[\text{MPn}_4]^{n-}$ (M = Nb, Ta, W, Ti).^[5] The two exceptions are Na_5HfAs_3 with dimers of edge-sharing tetrahedra of $[\text{Hf}_2\text{As}_6]^{10-}$ and $\text{Rb}_5\text{TaAs}_4\text{Ti}_2$ with $[\text{TaAs}_4]$ tetrahedra, where two Ti atoms bridge opposite edges, $(\mu\text{-Ti})\text{-}[\text{As}_2\text{TaAs}_2](\mu\text{-Ti})^{5-}$.^[6] Here we report a new d^0 transition metal Zintl phase, $\text{Cs}_7\text{NbIn}_3\text{As}_5$, which contains an unprecedented anion, $[\{\text{In}_3\text{As}_4\text{Nb}\}-\text{As}]^{7-}$, a cubane made of three indium, four arsenic, and one niobium atom and a “handle” composed of an arsenic atom that is multiply bonded to the niobium corner.

The title compound was initially made in an attempt to synthesize the recently reported $\text{Cs}_5\text{In}_3\text{As}_4$ at temperatures higher than the original 500 °C.^[7] The reaction was carried out in niobium containers at 800 °C, at which temperature the arsenic apparently attacked the container and formed the quaternary compound $\text{Cs}_7\text{NbIn}_3\text{As}_5$. Later it was synthesized in high yield using the corresponding elements in stoichiometric ratio at the same temperature.^[8]

The overall structure of $\text{Cs}_7\text{NbIn}_3\text{As}_5$ is quite simple and unremarkable,^[9] an ionic assembly of isolated anions of $[\text{NbIn}_3\text{As}_5]^{7-}$ immersed in a “sea” of cesium cations that screen them from each other (inter-anion $d_{\text{min}} = 5.009(4)$ Å). What is remarkable is the structure and bonding of the anion (Figure 1). Its geometry can be viewed in a few different ways. The more obvious approach is to recognize the cubane shape made of one Nb, three In, and four As atoms, $[\text{NbIn}_3\text{As}_4]$, and its “handle” of a fifth arsenic atom attached to the niobium

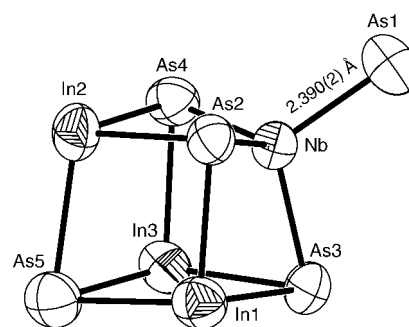


Figure 1. Structure of the cubane with a “handle” $[\{\text{As}(\text{InAs}_3)\text{Nb}=\text{As}\}]^{7-}$ (ORTEP drawing; thermal ellipsoids at the 95% probability level). The unusually short distance of the handle is shown. The remaining distances [Å] are: Nb–As2 2.484(2), Nb–As3 2.526(2), Nb–As4 2.535(2), In1–As2 2.834(2), In1–As3 2.794(2), In1–As5 2.908(2), In2–As2 2.864(2), In2–As4 2.789(2), In2–As5 2.894(2), In3–As3 2.845(2), In3–As4 2.822(2), In3–As5 2.858(2). The angles [°] at Nb and As5 are in the range 107.26(7)–112.82(7) and 79.32(5)–80.27(5), respectively. The angles around As2, As3, and As4 fall in the range 78.15(6)–82.09(5)°. The angles at the indium atoms that involve As5, 98.34(5)–99.28(6)°, are larger than those that do not, 91.25(5)–92.20(5)°.

[*] Prof. S. C. Sevov, F. Gascoin
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 (USA)
Fax: (+1) 219-631-6652
E-mail: ssevov@nd.edu

[**] This work was supported by the National Science Foundation (CHE-0098004). We also thank the Petroleum Research Fund, administered by the ACS, for partial support of this research.

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corner of the cube (Figure 1). Cubane is quite a popular shape especially for combinations of four transition metal (M) and four chalcogen (Ch) atoms, M_4Ch_4 .^[10] Recently reported was also a main group cation with the same geometry, $[Bi_4Te_4]^{4+}$.^[11] In all of these systems the two atom types alternate at the cubane corners providing equidistant M–Ch edges. In $[NbIn_3As_4]$, however, the cubane is uneven as one vertex is occupied by a niobium instead of an indium atom (Figure 1). Thus, three of the cubane edges are Nb–As bonds that are shorter ($d_{av} = 2.520 \text{ \AA}$) than the In–As bonds of the remaining nine edges ($d_{av} = 2.842 \text{ \AA}$). This leads to substantial distortion of the cube such that the niobium corner becomes closer to the cubane center than the other corners, and the rest of the cubane is compressed around the Nb–As5 body diagonal (Figure 1). All angles at As5 are, for example, noticeably smaller than 90° , while those at Nb and the As5–In–As angles are larger than 90° . The In–As distances are longer than those of four-bonded indium atoms in $Cs_5In_3As_4$, $K_4In_4As_6$, and Na_3InAs_2 ($d_{av} = 2.70 \text{ \AA}$),^[7, 12] but are closer to the distances of similarly three-bonded indium atoms in $Cs_5In_3As_4$ ($d_{av} = 2.90 \text{ \AA}$).^[7] The elongation is very likely due to the stronger repulsion between the lone pair at the three-bonded indium and the one or more lone pairs at the arsenic atoms.

exo-Bonded to the cubane at the niobium vertex is the fifth arsenic atom (As1) with a very short distance of $2.390(2) \text{ \AA}$. This clearly indicates a multiple Nb–As bond, which, in turn, is the basis for another way to view the anion. It can be described as tetrahedral niobium center coordinated by one tridentate, cage-like ligand of $[As(InAs)_3]$, and one single arsenic atom, $[As(InAs)_3]NbAs$. Such a description is justified by the fact that exactly the same cage-like, semicubane ligands have been already observed in $Cs_5[As(InAs)_3]$, in which they are connected in chains and layers through In–As and In–In *exo*-bonds.^[7] When viewed in this way (Figure 2a), the anion resembles known molecules with multiple bonds such as $[N(CH_2CH_2(Me_3Si)N)_3]W \equiv As$ ($d(W-As) 2.290(1) \text{ \AA}$; Figure 2b),^[13] $[(tBu_3SiO)_3Ta=As-Ph]$ ($d(Ta-As) 2.428(2) \text{ \AA}$; Figure 2c),^[14] and $[(Cp)_2[H(Tol)][Fe(CO)_4]As]Nb=As(Tol)-[Fe(CO)_4]$ ($d(Nb-As) 2.516(2) \text{ \AA}$; Figure 2d).^[15] The multiple

bonding in the above compounds and in $[As(InAs)_3]Nb-As]^{7-}$ is based on the π interactions between the empty d_{xz} and d_{yz} orbitals on the transition metal and the filled p_π orbitals on the arsenic center. Furthermore, while the two arsenidines $[L_3Ta=AsPh]$ and $[L_3Nb=AsTol]$ are bent at the arsenic and indicate sp^2 hybridization (maximum bond order of 2), the naked arsenide ligand can be viewed as sp -hybridized where both p_x and p_y orbitals are available for π interactions. This is the only arsenic atom in $[As(InAs)_3]Nb-As]^{7-}$ that is capable of π interactions with the Nb d orbitals, since the arsenic atoms of the tridentate ligand are “forced” to be sp^3 -hybridized. This results in the very short distance of $2.390(2) \text{ \AA}$, and the bonding can be schematically represented as a hybrid of $(\eta^3-L)M \equiv As \leftrightarrow (\eta^3-L)M^+=As^- \leftrightarrow (\eta^3-L)M^{2+}=As^{2-}$. For comparison, the average Nb–As distance of $2.50 \text{ \AA}$ in the tetrahedral $[NbAs_4]^{7-}$ ion is longer because all four arsenic atoms are capable of π interactions.^[5] According to molecular orbital analysis the bond order for each bond in tetrahedral d^0 species such as the latter is 2.25 (nine available bonding molecular orbitals), while it is 3.00 for tetrahedral species in which only one of the ligands has p_π orbitals such as the single arsenic center in $[As(InAs)_3]Nb-As]^{7-}$.^[16] Such an interpretation of the bonding is in better agreement with the observed extremely short distance of $2.390(2) \text{ \AA}$. Also, when compared to the much longer single Nb–As bond length of $2.720(1) \text{ \AA}$ in $[Cp_2H_2Nb-AsEt_2]$,^[17] this short distance corresponds indeed to a triple Nb–As bond.

The electron count and the charge of the anion can be accounted for by utilizing Zintl’s approach in which atoms achieve an octet by bonding or by additional negative charge. Thus, the cage-like tridentate ligand $[As(InAs)_3]$ has a formal charge of 9^- – made of three three-bonded In^{2-} ($3b-In^{2-}$), and one three-bonded As^0 ($3b-As^0$) and three two-bonded As^- ($2b-As^-$) atoms. Of course, these formal charges are assigned for the sole purpose of electron counting, and do not represent the real charges accumulated on the atoms. The cage and the isolated As^{3-} ion are coordinated to a Nb^V center to produce the resulting cubane with a handle $[(3b-As^0)(3b-In^{2-})_3(2b-As^-)_3]Nb^V(As^{3-})$. Conversely, one can apply a different formalism in which the indium atoms are In^I and all arsenic atoms are As^{3-} . This gives the same overall charge of 7^- for the anion. This charge is neutralized by the seven cesium cations of the formula, and, therefore, the compound is electronically balanced, a Zintl phase. This was confirmed by the magnetic measurements which indicated a diamagnetic, saltlike compound.^[18]

Received: October 15, 2001 [Z18059]

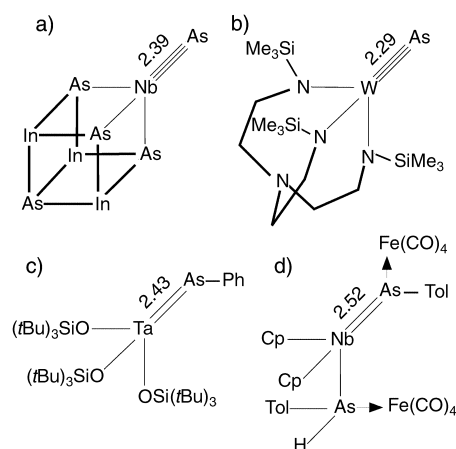


Figure 2. Species with similar coordination around the transition metal: a) $[As(InAs)_3]Nb=As]^{7-}$, b) $[N(CH_2CH_2(Me_3Si)N)_3]W \equiv As$; c) $[(tBu_3SiO)_3Ta=As-Ph]$, and d) $[(Cp)_2[H(Tol)][Fe(CO)_4]As]Nb=As(Tol)-[Fe(CO)_4]$.

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- [9] Selected crystals of the compound were mounted in glass capillaries (inside a dry box) and checked for singularity on a Bruker-APEX single crystal diffractometer with a CCD area detector (Mo_{Kα} radiation, $\lambda = 0.71073$ Å). Data were collected on the best one (irregular, $0.39 \times 0.37 \times 0.20$ mm) at room temperature ($2\theta_{\text{max}} = 50^\circ$), and were corrected for absorption (SADABS). The structure was solved in the triclinic space group $P\bar{1}$ and refined (on F^2) with the aid of the SHELXTL-V5.1 software package. Crystal data: triclinic, $P\bar{1}$, $a = 8.8101(9)$, $b = 9.664(1)$, $c = 14.748(2)$ Å; $\alpha = 85.421(2)$, $\beta = 85.961(2)$, $\gamma = 86.421(2)^\circ$, $V = 1246.5(2)$ Å³; $Z = 2$; $\mu = 198.28$ cm⁻¹; $\rho_{\text{calc}} = 4.642$ g cm⁻³. The refinement converged at $R1/wR2 = 0.0546/0.1409$ for 3424 observed reflections ($I > 2\sigma_i$) and 145 variables. Further details of the crystal structure investigation may be obtained from Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldsdorfen, Germany (fax: (+49)7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository number CSD-412274.
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- [18] The magnetization of Cs₇NbIn₃As₆ was measured on a quantum Design SQUID magnetometer at a field of 3 T over the temperature range 10–250 K. Selected crystals of the compound were ground to a powder (35 mg) which was then sealed in a fused-silica tubing between two tightly fitting rods of the same material. After corrections for the holder and for the ion-core diamagnetism the molar magnetic susceptibility was negative and temperature-independent varying between -1.4×10^{-4} and -1.7×10^{-4} emu mol⁻¹.

Surface Structure and Crystal Growth of Zeolite Beta C**

Ben Slater,* C. Richard A. Catlow, Zheng Liu, Tetsu Ohsuna, Osamu Terasaki, and Miguel A. Camblor

Zeolite Beta is a high silica zeolite that has attracted considerable experimental and theoretical investigation. In the seminal work of Newsam et al.^[1] and Higgins et al.,^[2] the crystal structure of zeolite Beta was deduced and three distinct polytypes were identified. Polymorph A is tetragonal and exists as an enantiomorphic pair of crystal structures. Structure B is monoclinic and achiral, whilst polytype C was predicted to be an achiral tetragonal phase. Until very recently, polymorph C had not been observed experimentally, but recent work^[3] described a proven synthetic route to this phase; furthermore, using novel methods based upon electron microscopy, the crystal structure was deduced. Herein, we focus attention from the bulk to the surface properties of this topical microporous material. By a combination of computer modeling with high-resolution electron microscopy (HREM), we are able to develop detailed models for the surface termination of this material and to gain new insight into the mechanism of its growth.

The purpose of the work described here is twofold: first we report a simulation using interatomic potential techniques of the zeolite Beta C surface structure, which is able to distinguish between many numerous possible terminations and support the HREM observations reported recently by Liu et al.^[3] Second, by inspection of the surface structure and analysis of the relative energies of formation using first principles methods, we present evidence that relates the growth mechanism to the external surface structure.

An interesting question that arises from addressing the surface structure of zeolites is that of how to discriminate between the relative stability of various faces and the huge

number of surface terminations that could arise during crystal growth of the microporous structure. The problem is made more difficult by the fact that there are relatively few examples of purely siliceous zeolites, the majority being aluminosilicates with varied aluminum, extra-framework cation, and water content. Aside from the quite general interest in zeolite Beta C, it is also apposite in that it provides a convenient means of evaluating the surface structure of a purely siliceous material, where questions about aluminum zoning and possible cation segregation effects do not arise and for which particularly well-resolved HREM data is available.

We have used atomistic methods based upon the Born model of solids and the forcefield of Sanders et al.^[4] This forcefield is particularly successful at reproducing the bulk lattice and vibrational properties of a wide range of siliceous materials, ranging in density, for example, from quartz to faujasite. The interatomic potentials are also of sufficient quality to derive surface structures and energetics as is evident from our recent work on the (111) surface of faujasite.^[5]

Using this parameter set, we relaxed the Beta C unit cell and its contents to zero force until the cell was in mechanical equilibrium, using the GULP program.^[6] Using a Donnay–Harker^[7] approach, the (100) face is found to have the largest interlayer distance (d_{hkl}) and would therefore be expected to dominate the morphology. Large plane separations are associated with weak interlayer binding and thus slow growing, morphologically important faces. Using a two-region strategy to simulate the surfaces (using the MARVIN code as described elsewhere^[8]), we are able to determine the surface energy, which can be readily used to discriminate between the stability of particular terminations and crystal faces. Using this criterion, we distinguished three possible (100) terminations as the most energetically favorable surfaces. Relaxation of four layers of the (100) face on a further four layers that are held fixed at the bulk equilibrium geometry gave essentially identical surface energies for the three different cuts (where the surface energies differed from each other by only 0.02 J m^{-2}). This result indicates that the surfaces are of equal thermodynamic stability with respect to the crystal bulk. The relaxed surface structures are shown in Figure 1, 2, and 3.

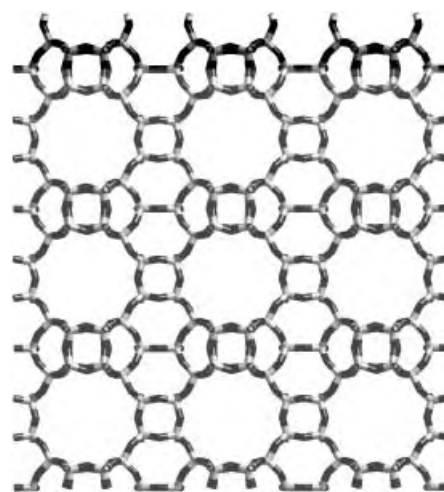


Figure 1. The type I surface of zeolite Beta C. Color code: Si: gray, O: black; H: white. The surface is shown in *cross section*. The greyed section is the zeolite surface continuum, the darker area is the growth surface.

[*] Dr. B. Slater, Prof. C. R. A. Catlow
Davy Faraday Research Laboratory
The Royal Institution of Great Britain
21 Albemarle Street, London, W1S 4BS (UK)
Fax: (+44)207-629-3569
E-mail: ben@ri.ac.uk

Dr. Z. Liu
CREST, Japan Science and Technology Corporation
Tohoku University
Sendai 980-8578 (Japan)

Dr. T. Ohsuna
Institute for Materials Research
Tohoku University
Sendai 980-8577 (Japan)

Prof. O. Terasaki
Department of Physics and CIR
Tohoku University
Sendai 980-8578 (Japan)

Dr. M. A. Camblor
Industrias Químicas del Ebro
Polígono de Malpica calle D. no. 97, 50057 Zaragoza (Spain)

[**] This work was supported by computing time made available by EPSRC (UK).

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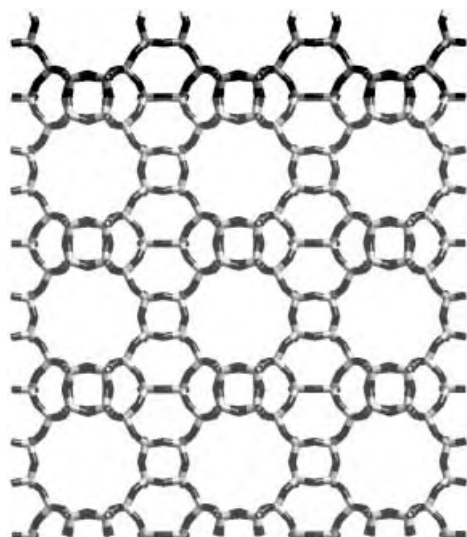


Figure 2. The type II surface of zeolite Beta C. Color code as in Figure 1.

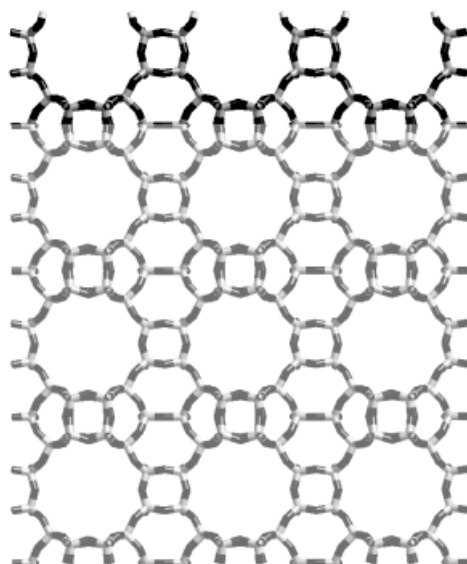


Figure 3. The type III surface of zeolite Beta C exhibiting a D4R structure. Color code as in Figure 1.

To compare these structures with our recent experimental data, we have constructed a montage (Figure 4). Figure 4a is the HREM of a single crystal of zeolite Beta C, and Figure 4b and c are magnified sections of a), exposing two distinct terminations. The simulated HREM images in Figure 4d–f have been calculated from the three relaxed terminations shown in Figure 4g, h, and i (which depict the silica framework of Figure 1, 2, and 3). What is immediately obvious by comparison with experimental HREM images shown in Figure 4b and c is that the predicted terminations agree perfectly with the measurements. Figure 1 and 4b are the type I surface proposed by us^[3] which is relatively topologically smooth. Figure 3 and 4c clearly exhibit a double 4-ring (D4R) and correspond with the type III surface.

The type II surface (Figure 2) is not observed in the experimental HREM image. However on energetic grounds, this surface would be expected to be stable.

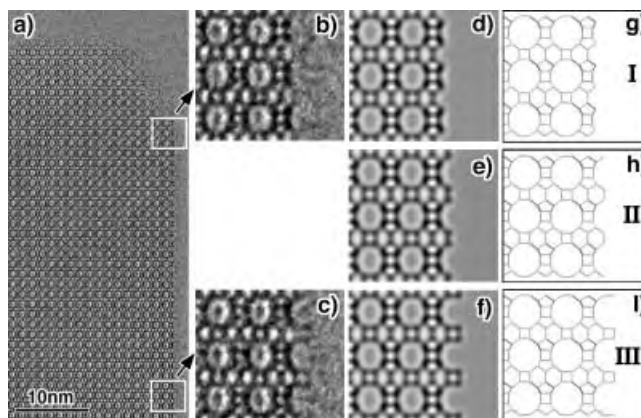


Figure 4. a), b), c) Composite of HREM images.^[3] d), e), f) Simulated HREM images from relaxed surface structures g), h), and i), respectively, corresponding to a 90° rotation of the type I, II, and III surfaces shown in Figure 1, 2, and 3, respectively.

Upon inspection, the type II surface is related to the type I and type III terminations by the addition or removal of a single silicon 4-ring (S4R), respectively (by a condensation reaction). Intuitively, one recognizes that the terminations form part of a sequence that corresponds to a crystal growth process. To resolve this apparent discrepancy between theory and experiment, we assessed the feasibility of crystal growth by reacting elementary siliceous growth units with the type I surface, to form the type II and type III terminations.

We performed density functional theory, total energy pseudopotential calculations using the CASTEP^[9] code on a single layer of the (100) face, starting from the type I termination. Details of the parameters used and simulation conditions are available as Supporting Information. We initially considered two possible mechanistic routes leading to the formation of the two observed terminations. In the first strategy shown in Figure 5, we consider direct condensation of a S4R on the type I surface to give the type II surface (reaction A), followed by further condensation of a S4R, to give the type III surface (reaction B). Figure 6 depicts the direct condensation of a D4R unit on the type I surface, resulting in the formation of the type III surface (reaction C). In each instance, the total energies of formation for the reactant and products in their ground state were used to calculate the net change in enthalpy.

Reaction A is calculated to be an endothermic process. As an additional check on the reliability of this key result, we performed the same calculation but with a broken 4-ring (B4R), which has been shown previously^[10] to possess a higher condensation energy than the S4R. The direct condensation of monomers and dimers was also considered. In each case, reaction A was found to be endothermic which suggests that the reaction does not proceed or it occurs by a different reaction pathway. Irrespective of this evidence, if termination II is formed by whatever pathway, reaction B (calculated with respect to a S4R) is thermodynamically favorable and therefore termination II is thermodynamically and probably kinetically unstable with respect to termination III. By contrast, reaction C is predicted to be only slightly energeti-



Figure 5. The S4R-mediated reaction pathway. The reaction proceeds by the addition of an S4R to the type I surface, giving the type II surface and further S4R condensation to give the type III surface. Color code as in Figure 1.

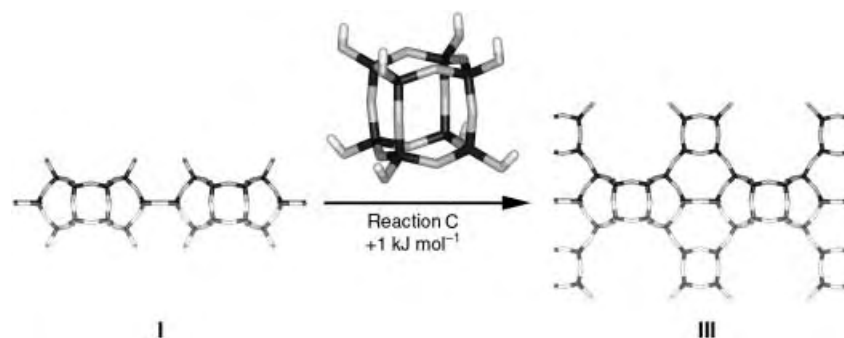


Figure 6. The D4R-mediated reaction pathway. The reaction proceeds by a one-step condensation of a D4R species onto the type I surface to give the type III surface. Color code as in Figure 1.

cally unfavorable but even at relatively moderate temperatures, this reaction would be expected to proceed.

Given these findings, the evidence suggests that termination II, the surface structure expected to be stable on the grounds of surface energy, but not observed by HREM,^[3] is either not formed, or quickly reacts to give the D4R-terminated surface. By contrast, condensation of a D4R unit on the type I surface is predicted to occur under reaction conditions. The addition of this unit gives a route from the type I to type III surface, which does not require formation of the type II surface and therefore may also explain why the type II surface is not observed. Given recent synthetic findings, the process of condensation which gives rise to the D4R unit is clearly accelerated by the presence of fluoride ions. We speculate that the fluoride ion lowers the activation barrier that separates reagents from the D4R unit and other products but will address this point directly in future work.

In summary, we have demonstrated that relatively simple interatomic potential calculations are able to reproduce the surface structures observed by using HREM imaging. Additionally, direct assessment of the crystal growth process reveals that one possible termination is not formed or is likely to be a short-lived intermediate that accounts directly for its absence in HREM imaging experiments. More fundamentally, the results provide evidence that the nanoscopic surface structures arise not simply from optimal packing of silicate tetrahedra but from the complex reactions of siliceous oligomers with the zeolite surface.

Received: October 17, 2001
Revised: February 14, 2002 [Z18075]

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Pd-Catalyzed Decarbonylative Olefination of Aryl Esters: Towards a Waste-Free Heck Reaction**

Lukas J. Gooßen* and J. Paetzold

*Dedicated to Dr. Manfred Jautelat
on the occasion of his retirement*

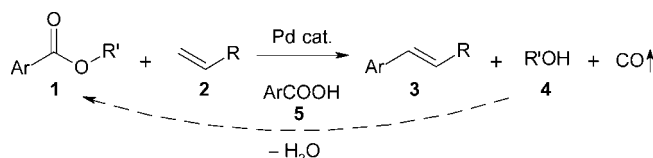
Over the last years, the Heck reaction has found widespread use in preparative laboratories and in industrial applications as a mild and efficient method for the regioselective attachment of side chains to aromatic rings.^[1] Besides the standard aryl halides, various aryl sources such as aryl triflates,^[2]

[*] Dr. L. J. Gooßen, J. Paetzold
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2985
E-mail: goossen@mpi-muelheim.mpg.de

[**] We thank L. Winkel for technical assistance, Prof. Dr. M. T. Reetz for generous support and constant encouragement, and the DFG, the FCI, and the BMBF for financial support.

diazonium salts,^[3] sulfonyl halides,^[4] and aroyl halides^[5] have been utilized, and highly efficient catalyst systems have been developed.^[6] However, for all these compounds, stoichiometric amounts of base are required, and the equivalent amounts of waste salts are produced. De Vries and co-workers first presented a possible solution to this long-standing problem when they utilized aromatic carboxylic acid anhydrides as aryl sources.^[7] In the presence of a PdCl₂/NaBr catalyst system, carboxylic anhydrides were cleanly converted into one equivalent of the corresponding vinyl arenes and one equivalent of the carboxylic acids, which, in principle, can be converted back into the starting anhydride. However, for most carboxylic acids, the dehydration reaction does not occur readily and is usually not waste-free either.^[8]

Herein we report the first example of a Heck reaction in which the by-product can be recycled efficiently so that only CO and water are produced as waste. Our strategy to make efficient use of the widely available carboxylic acids as substrates for the Heck reaction while overcoming the limitations of the previous protocols was to perform the olefination with carboxylic acid derivatives that are less reactive and more easily accessible than anhydrides, that is, with esters.^[9] We found a palladium catalyst that is able to insert into the carbon–oxygen bond of an ester, thus entering a catalytic cycle similar to the one postulated for the Heck reaction of carboxylic acid anhydrides.^[7, 10] After the oxidative addition of the ester to the palladium center, extrusion of carbon monoxide leads to the formation of an aryl–palladium complex, and after insertion of the olefin, β -hydride elimination liberates the desired vinyl arene and the alcohol by-product. The alcohol can then be recycled back into the starting ester by reaction with fresh carboxylic acid by using standard esterification techniques (Scheme 1). In this case,



Scheme 1. Decarbonylative Heck olefination of esters.

CO and water are the only by-products in the overall reaction.

The key step towards realizing this highly desirable process was to identify a catalyst system capable of activating carboxylic esters. We thus screened various catalysts under different conditions for the model reaction of *p*-nitrophenyl benzoate (**1a**) and styrene **2a** (Scheme 1, Ar = Ph, R = Ph, R' = *p*-NO₂C₆H₄). *p*-Nitrophenyl esters are particularly attractive substrates because they can be generated within minutes in quantitative yields from various functionalized carboxylic acids and commercially available nitrophenyl chloroformate.^[11] Selected results of our screening experiments are shown in Table 1.

Palladium chloride was identified to be the best precatalyst (Table 1, entries 1–3), and the addition of alkali metal halides proved to increase the effectiveness of the catalyst further (Table 1, entries 4–11).^[7, 12] Among these, the cheap and easily separable lithium chloride was found to be as effective

Table 1. Reaction of nitrophenyl benzoate with styrene.

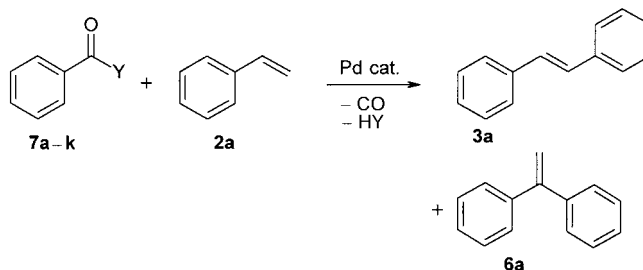
Entry	Pd source	Additive	Ligand	Conversion [%]	Selectivity [%]
1	Pd(OAc) ₂	–	–	< 2	> 90
2	(dba) ₃ Pd ₂	–	–	< 2	> 90
3	PdCl ₂	–	–	12	90
4	PdCl ₂	LiCl	–	60	> 95
5	PdCl ₂	LiBr	–	39	> 95
6	PdCl ₂	KCl	–	24	> 95
7	PdCl ₂	KBr	–	30	> 95
8	PdCl ₂	NaCl	–	31	> 95
9	PdCl ₂	NaBr	–	35	> 95
10	PdCl ₂	TBACl	–	36	90
11	PdCl ₂	TBABr	–	56	90
12	PdCl ₂	LiCl	PPh ₃	22	75
13	PdCl ₂	LiCl	Picoline	69	> 95
14	PdCl ₂	LiCl	Quinoline	67	80
15	PdCl ₂	LiCl	Isoquinoline	91	> 95
16 ^[a]	PdCl ₂	LiCl	Isoquinoline	44	> 95

Conditions: nitrophenyl benzoate (1 mmol), styrene (1.2 mmol), Pd source (0.03 mmol), additive (0.09 mmol), ligand (0.1 mmol), NMP, 16 h, 160 °C. Conversions and selectivities were determined by GC analysis, with tetradecane as internal standard. [a] The reaction was performed with 0.3 mol % catalyst. NMP = *N*-methylpyrrolidone.

as tetra-*n*-butylammonium bromide (Table 1, entries 4, 11). Without the addition of stabilizing ligands, the reaction initially proceeded with a fast turnover. However, complete precipitation of the catalyst and loss of catalytic activity was observed before full conversion of the substrate. The addition of amines significantly slowed down the reaction, but greatly enhanced the stability of the catalyst so that higher yields were obtained (Table 1, entries 13–15). The starting material was almost fully converted within a reasonable reaction time when isoquinoline or substituted pyridines were used as ligands. Phosphanes coordinate more strongly and therefore inhibit the reaction (Table 1, entry 12).

The ideal amount of catalyst is 3 mol %, but even with a significantly lower catalyst loading, moderate yields are obtained (Table 1, entry 16). Similarly to the standard Heck olefinations, the olefin did not insert into the aryl–palladium bond with complete regioselectivity, so that in all cases a 13:1 mixture of the products **3a** and **6a** was obtained (Scheme 2).^[13]

We next investigated the range of acid derivatives that can be converted with the optimized catalyst system (Scheme 2; Table 2). Benzoates of various electron-deficient phenols were found to be suitable substrates (Table 2, entries 1–4). Expectedly, the ester of highly acidic pentafluorophenol is most reactive, but reaction turnover was observed even with poorly activated *p*-CF₃-phenol (Table 2, entries 5). Unfortu-



Scheme 2. Decarbonylative Heck olefination of benzoic acid derivatives.

Table 2. Variation of the benzoic acid derivative.

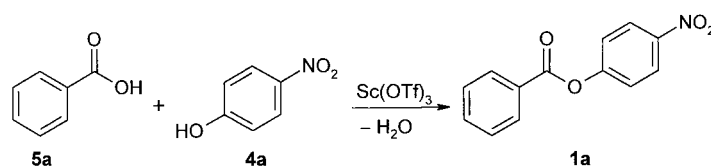
Entry	Y	Yield (3+6) [%] ^[a]	Entry	Y	Yield (3+6) [%] ^[a]
1		94	7	O-CH ₃	–
2		53	8		51
3		30	9		68
4		77	10		25
5		13	11		10
6		trace	12		10 ^[b]

Conditions: benzoic acid derivative (1 mmol), styrene (1.2 mmol), PdCl₂ (0.03 mmol), LiCl (0.09 mmol), isoquinoline (0.3 mmol), NMP, 16 h, 160 °C. [a] The yields were determined by GC analysis, with tetradecane as internal standard. In all cases, except entry 12, 13:1 mixtures of the isomers **3** and **6** were formed in >95 % selectivity; [b] Full conversion, isobutene was the main product.

nately, only trace amounts of product were observed in the reactions with esters of alkanols or phenol itself (Table 2, entries 6, 7).

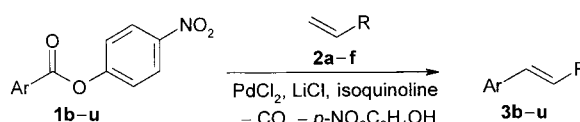
Besides phenol esters, acid derivatives with similar activity, for example, hydroxysuccinimides and imidazolides, were also converted by the catalyst system in reasonable yields (Table 2, entries 8–10). Vinyl esters would have been particularly interesting substrates since the volatile acetaldehyde is the only by-product in the olefination reaction. However, only modest conversions were observed for this type of substrate (Table 2, entry 11). Surprisingly, the mixed anhydride of benzoic acid and pivalic acid, which was successfully employed in other Pd-catalyzed reactions,^[14] did not react with the desired regioselectivity: instead of stilbene and pivalic acid, isobutene and benzoic acid were the main products (Table 2, entry 12).

To demonstrate the viability of our concept for a waste-free Heck olefination, we looked for a catalytic method to generate activated *p*-nitrophenyl esters directly from carboxylic acids and the alcohol, hence avoiding the use of stoichiometric amounts of a dehydrating agent. We screened several esterification catalysts under various conditions for the model reaction of nitrophenol with benzoic acid (Scheme 3). Although only moderate yields were observed with standard dehydration catalysts,^[15] for example, sulfuric acid (61 %), *p*-toluenesulfonic acid (45 %), or HfCl₄ (5 %), the desired conversion gave good yields in the presence of Sc(OTf)₃ (3 mol %) at 160 °C in the absence of solvent (83 %) or in *o*-dichlorobenzene (56 %). Thus, nitrophenol is recycled and a waste-free process is possible.



Scheme 3. Conversion of benzoic acid into the nitrophenol ester.

The scope of the new Heck olefination was investigated by using various combinations of *p*-nitrophenyl carboxylates and olefins (Scheme 4, Table 3). Electron-deficient carboxylic

Scheme 4. Heck olefination of *p*-nitrophenyl carboxylates.

esters were found to react faster and to give better yields than electron-rich derivatives, but even the electron-rich *p*-MeO-stilbene is still accessible in a satisfactory yield (Table 3, entry 1). Many functional groups are tolerated: carboxylic esters that contain halo, keto, cyano, formyl, nitro, or protected amino groups were successfully converted (**3a–m**). The important class of heterocyclic carboxylic esters was also suitable as starting materials (**3n**, **3o**). The decarbonylative Heck olefination of the widely available α,β -unsaturated carboxylic esters (**3p**) could also be particularly useful, since the availability of the synthetically equivalent vinyl halides is rather limited.

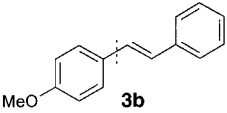
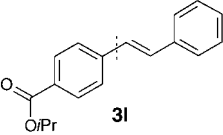
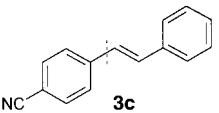
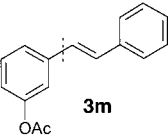
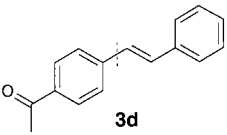
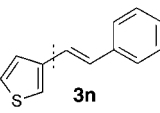
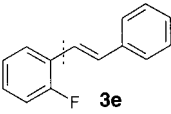
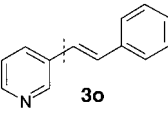
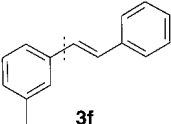
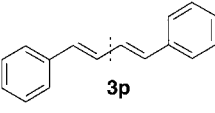
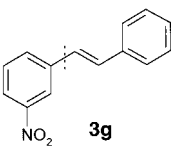
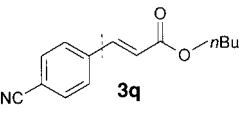
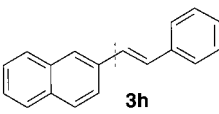
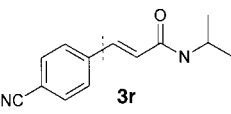
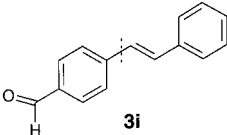
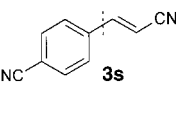
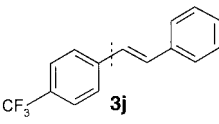
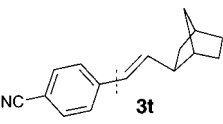
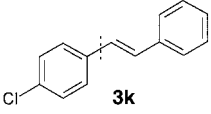
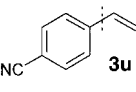
Various olefins are suitable substrates (**3q–u**). Both electron-rich and electron-poor olefins give similar yields. Even styrene derivatives are conveniently accessible in good yields when trimethylvinylsilane is used as an ethylene surrogate (**3u**).^[16] However, similarly to conventional Heck olefinations, the addition is not always completely regioselective; in some cases, Pd-catalyzed double-bond isomerization leads to the formation of complex product mixtures (**3q**).

In summary, the palladium-catalyzed Heck olefination disclosed herein represents a simple, high-yielding synthesis of functionalized vinyl arenes, heteroarenes, and 1,3-dienes from the plethora of available carboxylic acids via their nitrophenol esters. The nitrophenol esters are conveniently accessible from carboxylic acids and nitrophenol chloroformate. The alternative possibility of generating them directly from carboxylic acids and nitrophenol allows a low-waste reaction protocol for Heck olefinations. Further improvements of the catalytic system aiming at the conversion of esters of alkanols or phenol are under investigation in our research group.^[17]

Experimental Section

Synthesis of 1: A 50-mL flask was charged with the carboxylic acid (15 mmol), triethylamine (20 mmol), and dichloromethane (30 mL). Solid nitrophenyl chloroformate (3.02 g, 15 mmol) was added slowly, and the reaction mixture was stirred for a few minutes until gas evolution ceased. The reaction mixture was then filtered through a plug of basic aluminum oxide with dichloromethane as eluent. After recrystallization from hexane/

Table 3. Scope of the Heck olefination.

Product	Yield ^[a]	3/6 ^[b]	Product	Yield ^[a]	3/6 ^[b]
 3b	54 (60)	9:1	 3l	70 (85)	13:1
 3c	83 (99)	14:1	 3m	40 (60)	13:1
 3d	85 (99)	13:1	 3n	47 (53)	10:1
 3e	79 (96)	13:1	 3o	90 (98)	13:1
 3f	52 (53)	9:1	 3p	83 (83)	13:1
 3g	55 (60)	13:1	 3q	95 (99)	20:1
 3h	80 (85)	10:1	 3r	67 (90)	13:1
 3i	85 (98)	15:1	 3s	86 (98)	5:1
 3j	74 (98)	15:1	 3t	86 (92)	4:1 ^[c]
 3k	88 (95)	20:1	 3u	62 (64)	–

Conditions: nitrophenyl ester (1 mmol), olefin (1.2 mmol), PdCl₂ (0.03 mmol), LiCl (0.1 mmol), isoquinoline (0.3 mmol), NMP, 160 °C, 16 h. [a] Yields of isolated products (yields determined by GC are shown in parentheses). [b] The distribution of the isomers **3** and **6** was determined by GC analysis of the crude reaction mixture. [c] Mixture with small amounts of double-bond isomers.

ethyl acetate, the *p*-nitrophenyl benzoates were obtained as colorless crystals in excellent yields (85–95 %).

Synthesis of 1a from 5a: A 20-mL reaction flask was charged with nitrophenol (417 mg, 3 mmol), benzoic acid (244 mg, 2 mmol), and scandium triflate (29.5 mg, 0.06 mmol) and was fitted to a tube filled with molecular sieves (4 Å, 300 mg). The mixture was heated to 160 °C for 5 h. The progress of the reaction was monitored by GC. After the reaction was complete, the dark mixture was purified by Kugelrohr distillation to yield the desired nitrophenyl benzoate **1a** (398 mg, 82 %).

Synthesis of 3a–u: A 20-mL reaction vessel was charged with the nitrophenyl ester **1a–u** (1 mmol), PdCl₂ (5.3 mg, 0.03 mmol), LiCl (4.3 mg, 0.1 mmol), isoquinoline (38 mg, 0.3 mmol), and NMP (5 mL). The olefin **2a–f** (1.2 mmol) was then added through a syringe, and the reaction vessel was sealed with a septum. The reaction mixture was degassed by bubbling argon through the solution and was then slowly heated to 160 °C. The progress of the reaction was monitored by GC. When the reaction was complete (usually after 5 h), the reaction mixture was taken up in toluene and was washed sequentially with water, HCl (0.5 M), and aqueous sodium bicarbonate. The organic layer was dried over MgSO₄,

filtered, and the volatile components were removed in vacuo. The residue was isolated by means of column chromatography (SiO₂, dichloromethane:hexane 1:1–10:1) and characterized by means of ¹H and ¹³C NMR spectroscopy as well as by GC/MS and HRMS.

Received: January 4, 2002 [Z18481]

Electron-Hole Pairs Stabilized in Al-ZSM-5 Zeolites**



Alain Moissette,* Hervé Vezin, Isabelle Gener, Joël Patarin, and Claude Brémard

Photoinduced electron transfer to yield charged-separated states is the most fundamental energy conversion process of the photovoltaic effect, exciton storage in semiconductors, and photosynthesis. Ionization of organic molecules on heterogeneous catalysts^[1, 2] is predicted to become an exciting area of research. However, practical applications are often hampered by a rapid back reaction. Inhibition of the undesirable back-transfer of electrons requires control of both electronic and spatial properties of the system. Photoinduced charge separation can be achieved by sophisticated molecular triads and higher analogues that are currently capable of producing a charge-separated state with good yield and a lifetime of less than 1 s.^[3] Microporous aluminosilicate materials such as zeolites provide an appropriate micro-environment to efficiently trap electrons.^[4, 5] The electron trapped in zeolites can be generated in different ways: 1) radiolysis using high-energy radiations, 2) photolysis of preadsorbed molecules, and 3) mere exposure of electron-donor compounds such as alkali metal vapor or organic compounds to dehydrated zeolites. It appears that the presence of heteroatoms such as aluminum in the siliceous framework and extra-framework cations is a requirement for efficient electron trapping.^[6, 7] Although the characterization of occluded organic radical ions has been established, the whereabouts of electrons within the inorganic supports remains unclear and is the subject of considerable debate.^[1, 2, 4, 5, 8] Surprisingly, aluminosilicate zeolites are also known to contain electron-donor sites capable of transferring electrons to strong acceptors. Herein, we characterize the unusual system of acidic Al-ZSM-5 zeolite loaded with biphenyl (BP, C₁₂H₁₀) groups in which both electron-acceptor

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[*] Dr. A. Moissette, Dr. C. Brémard

Laboratoire de Spectrochimie Infrarouge et Raman

UMR-CNRS 8516

Centre d'Etudes et de Recherches Lasers et Applications, Bât. C5

Université des Sciences et Technologies de Lille

59655 Villeneuve d'Ascq cedex (France)

Fax: (+33) 320-436-755

E-mail: alain.moissette@univ-lille1.fr

Dr. H. Vezin

Laboratoire de Chimie Organique et Macromoléculaire

ESA-CNRS 8009, Bât. C3

Université des Sciences et Technologies de Lille

59655, Villeneuve d'Ascq cedex (France)

Dr. I. Gener

Laboratoire de Catalyse en Chimie Organique, UMR-CNRS 6503

Université de Poitiers

40 avenue du recteur Pineau, 80022 Poitiers (France)

Dr. J. Patarin

Laboratoire des Matériaux Minéraux, ESA-CNRS 7016

Ecole Nationale Supérieure de Chimie de Mulhouse

3 rue Alfred Werner, 68093 Mulhouse cedex (France)

[**] The Centre d'Etudes et de Recherches Lasers et Applications (CERLA) is supported by the Ministère chargé de la recherche, the région Nord/Pas de Calais, and the Fonds Européen de Développement Economique des Régions.

and electron-donor capabilities of the zeolite are used to generate and stabilize ultrastable electron-hole pairs.

After removal of the template and water molecules from the framework of the as-synthesized ZSM-5 zeolites by a calcination procedure, the framework topology of ZSM-5, $H_n(AlO_2)_n(SiO_2)_{96-n}$, comprises a three-dimensional network of straight and sinusoidal channels.^[9] Brønsted acid sites were assigned to the bridging OH group of the Si-OH-Al moieties, and the Al atoms were assumed to be randomly substituted by Si. Special attention was paid to the purity of the as-synthesized zeolites as well as to the dehydrated bare acidic samples, even beyond impurity levels normally detected by conventional elementary analyses.^[10] After calcination of as-synthesized zeolites at 800 K under O_2 and subsequent rehydration, no extra-framework aluminum species were detected by ^{27}Al MAS-NMR spectroscopy for hydrated H_n ZSM-5 samples containing less than four Al atoms per unit cell. After another dehydration procedure under vacuum or argon or O_2 at 800 K and subsequent evacuation under vacuum, all the physicochemical measurements (powder X-ray diffraction, ^{29}Si MAS-NMR, EPR, Raman, UV/Vis, and IR absorption) provide clear evidence of pure bare ZSM-5 zeolites. In particular, no EPR signal corresponding to iron(III) ($g = 4.26$) or other paramagnetic impurities was detected in the spectra of the samples before exposure to biphenyl (BP).^[11] It should be noted that after the calcination procedure at 800 K under O_2 , the sharp bands assigned to the OH stretching mode of the Al-OH-Si unit broaden significantly with respect to those of an identical sample calcined under argon at the same temperature.

In the dark, BP molecules were sorbed as intact molecules as BP/ H_n ZSM-5 through exposure of weighted amounts of BP under argon to H_n ZSM-5 samples dehydrated under vacuum or argon. In contrast, spontaneous partial ionization of BP occurs when H_n ZSM-5 was calcined under O_2 . This striking phenomenon was detailed previously and used below.^[10, 12] The rod-shaped BP molecule can penetrate and self-assemble in the pores of the zeolite. In its energetically favorable site, BP lies in the straight channel in a twisted conformation, and diffusion was found to be slow at room temperature.^[13]

Laser photolysis of BP/ M_n ZSM-5 was investigated previously by transient absorption and time-resolved resonance-Raman spectroscopy on the nanosecond time scale.^[7] The photoionization generates primarily the biphenyl radical cation $BP^{+•}$ and a trapped electron, abbreviated as ZSM-5 $^{•-}$. Then, the electron-deficient $BP^{+•}$ captures another electron from the zeolite framework and regenerates neutral BP(S_0) in the ground state which leads to a so-called electron-hole pair, denoted as BP/ M_6 ZSM-5 $^{•-•+}$.^[7] No evidence was found for BP as an electron scavenger through the detection of the biphenyl radical anion $BP^{•-}$. The lifetimes of these transient species increase dramatically as the aluminum content of the ZSM-5 framework increases and were found to

depend highly on the nature of the extra-framework cations M .^[7] After the disappearance of the $BP^{+•}$ and the regeneration of occluded BP(S_0), the electron-hole was found to persist for one day at room temperature for high aluminum content and suitable extra-framework metal cations.^[7]

The presence of a proton as the counterbalancing cation in H_n ZSM-5 induced unusual behavior with regard to the formation and stabilization of electron-hole pairs from occluded BP.^[10, 13] The photolysis of BP/ H_n ZSM-5 zeolites under argon generates $BP^{+•}/H_n$ ZSM-5 $^{•-}$ and then finally the ultralong electron-hole pair BP/ZSM-5 $^{•-•+}$. Analogous stable electron-hole pairs were also obtained thermally through the mere exposure of BP under argon to H_n ZSM-5 obtained from calcination at 800 K under O_2 and subsequent evacuation under vacuum. Introduction of BP (one BP molecule per unit cell loading) turned the powder from white to blue and after one week the solids turned pink. Complete disappearance of $BP^{+•}$ and self-organization of the system required approximately one month. The samples obtained by the photochemical and thermal processes exhibit identical physicochemical characteristics; however, the thermal process allowed a better control of the unpaired electron density as well as a better homogeneity of the samples.

After the complete disappearance of the Raman bands of $BP^{+•}$, all the characteristic Raman frequencies of BP(S_0) in BP/ H_n ZSM-5 $^{•-•+}$ were observed in the spectra recorded at 370 and 1064 nm (Figure 1c). All the Raman features were found to be analogous in terms of wavenumbers and relative intensities to those of BP/ H_n ZSM-5 obtained by sorption in H_3 ZSM-5 dehydrated under argon for which spontaneous ionization does not occur (Figure 1b). It should be noted that the relative intensities differ markedly for BP in a nonpolar environment (silicalite-1; Figure 1a). These findings indicate low local symmetry and an intense electrostatic field at the sorption site. After the disappearance of the characteristic electronic absorption bands of $BP^{+•}$ at 370 and 650 nm, the

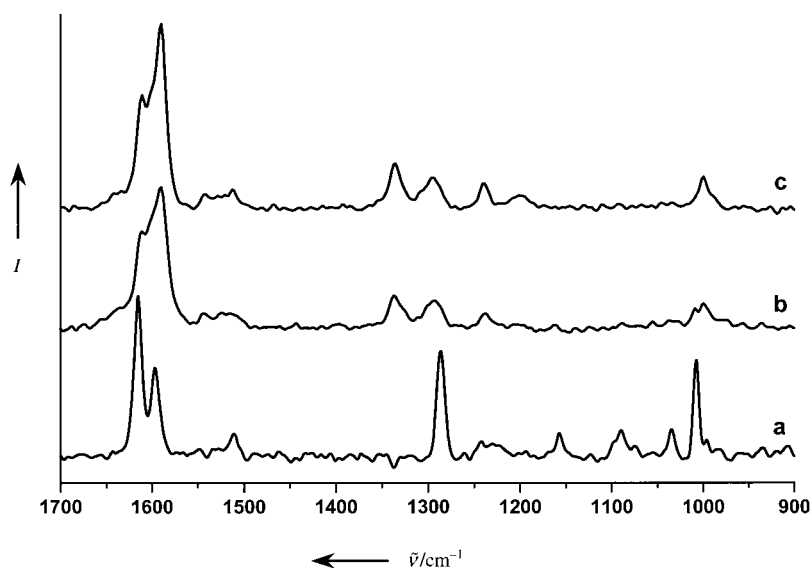


Figure 1. FT-Raman spectra (wavelength 1064 nm) of biphenyl (BP) occluded in silicalite-1, $(SiO_2)_{192}$ (a), in H_3 ZSM-5, $H_3(AlO_2)_3(SiO_2)_{189}$, dehydrated under argon (b), and in H_3 ZSM-5 $^{•-•+}$ after the disappearance of the radical cation $BP^{+•}$, $H_3(AlO_2)_3(SiO_2)_{189}$, activated under O_2 and evacuated under vacuum (c). I = Raman intensity in arbitrary units.

diffuse reflectance (DR)UV-Vis absorption spectrum exhibits an intense broad absorption around 500 nm in addition to the characteristic band at 250 nm displayed by occluded BP. No evidence of BP^{•-} (400, 610 nm) was observed. The persistent absorption at 500 nm was correlated with the appearance of a featureless continuous-wave (CW)-EPR signal (Figure 2); the seven-line spectrum of BP^{•+}[7, 10, 14] disappeared and was replaced by a broad signal around $g = 2$.^[10]

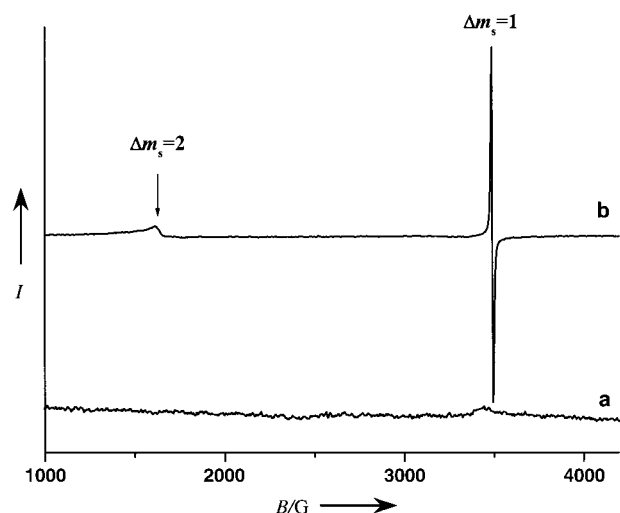


Figure 2. CW X-band EPR spectra of the H₃ZSM-5 zeolite calcined at 800 K under O₂ and evacuated under vacuum (a), and biphenyl occluded in the H₃ZSM-5^{•+} zeolite (one BP molecule per unit cell) six months after the sorption (b). The spectra were recorded at 100 K with a modulation amplitude of 1 G and at a microwave power of 10 mW.

The strong signal around $g = 2$, which is typical of BP/H_nZSM-5^{•+}, remains broad even at low temperature (Figure 2b). The EPR signal and electronic absorption were found to be persistent over at least one year. The densities of unpaired electrons were estimated by double integrals of the EPR signals to be 0.3, 1.0, and 7.0×10^{-2} per unit cell for BP/H_nZSM-5^{•+} with $n = 1, 2$, and 3, respectively, after several months under our experimental conditions. The electron-hole yield in BP/H_nZSM-5^{•+} increases with Al content and temperature of calcination under O₂. With a spin density of less than 7.0×10^{-2} per unit cell and an assumed random distribution, the unpaired electrons would be separated on average by more than 70 Å and no interaction would occur between the unpaired electrons. Applying CW-EPR as a function of temperature we were able to characterize the magnetic exchange coupling between unpaired electrons of BP/H_nZSM-5^{•+}. A weak signal at a g value of about 4.22 is clearly visible and can be attributed to the forbidden transition $\Delta m_s = 2$ in a spin triplet $S = 1$, resulting from an electronic spin-coupling interaction ($S = 1/2$). The Boltzmann fitting of $g = 2.0036$ to the double integral signal of several spectra recorded from 10 to 300 K yields a value for the magnetic coupling constant of approximately 0.2 cm^{-1} . This results from population of the triplet state at low temperature. Thus, there is no doubt that the occluded electron-hole pair acquires a ferromagnetic ground state. The coupling constant

estimates were not found to depend on the spin density, and the ferromagnetic exchange value is representative of individual electron-hole pairs in BP/H_nZSM-5^{•+}.

No hyperfine interaction was detected in the broad persistent signal of the CW-EPR spectra even at low temperature. To determine the structural surroundings of the unpaired electrons within BP/H₃ZSM-5^{•+} we performed pulsed EPR experiments. Electron spin echo envelope modulation (ESEEM) spectroscopy measures the energy splittings of nuclei whose spins interact with the spin of unpaired electrons. These energy splittings were used to determine the nature of the electron nucleus environments. Significantly higher resolution was achieved in a two-dimensional (2D) four-pulse, hyperfine sublevel correlation (HYSCORE) spectroscopy experiment.^[15–17]

The results of such an experiment are displayed in Figure 3a, which shows five ridges centered at a proton nuclear Larmor frequency of 14.5 MHz. We can directly measure an anisotropic hyperfine constant of 9 MHz. An additional peak centered at 2.9 MHz corresponds to a ²⁹Si free nuclear Larmor frequency resulting from a ²⁹Si nucleus coupling with an

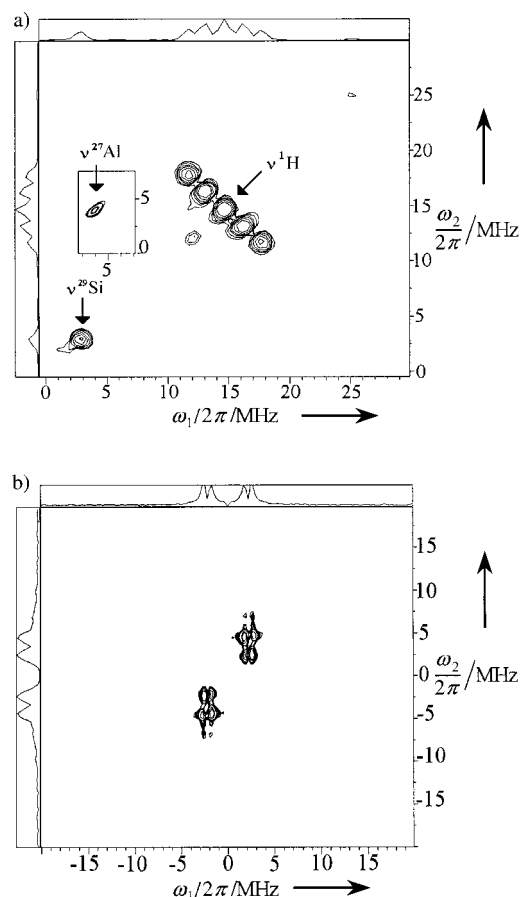


Figure 3. a) HYSCORE spectrum of an [H₁₀]biphenyl molecule occluded in the H₃ZSM-5^{•+} zeolite (1 BP/H₃ZSM-5) six months after the sorption. The spectrum was obtained at the maximum of the EPR signal at 300 K at $\tau = 256 \text{ ns}$ and at 4.2 K (framed) at $\tau = 200 \text{ ns}$. Pulse lengths of 12 ns for $\pi/2$ pulses and 24 ns for the π pulse were used, and a four-step phase cycling ($\pi/2 - \tau - \pi/2 - t_1 - \pi - t_2 - \pi/2 - \tau$ -echo) was applied to suppress unwanted echo. b) Two-dimensional, three-pulse ESEEM spectrum of [D₁₀]biphenyl occluded in the H₃ZSM-5^{•+} zeolite (1 BP/H₃ZSM-5) six months after the sorption. Pulse lengths of 12 ns were set for the $\pi/2$ pulses.

electron. When the experiments were carried out at 4.2 K another peak centered at 3.8 MHz can be assigned to the free Larmor nuclear frequency of ^{27}Al nuclei (see frame in Figure 3a). No coupling of a ^{13}C nucleus with an electron was detected. To establish the origin of the proton modulation, we performed the experiment with fully deuterated $[\text{D}_{10}]\text{BP}$. The substitution of the ^1H by the ^2H isotope in BP dramatically affects the two-dimensional, three-pulse ESEEM spectrum (Figure 3b). These findings indicate that the ^1H or ^2H isotope of BP are the main contributors to these lines. The proton modulation has effectively completely disappeared but a strong deuterium pattern is observed. The corresponding HYSCORE spectra (not shown) yield an anisotropic coupling constant of 1.6 MHz. In contrast, the substitution of ^1H by ^2H in the bridging OH group of the $\text{H}_3\text{ZSM-5}$ zeolite, and subsequent $[\text{H}_{10}]\text{BP}$ sorption does not affect the CW EPR spectrum. However, the two-pulse ESEEM spectrum reveals a strong ^1H pattern modulation with an overlapped weak ^2H pattern modulation. Removing proton modulation by high pass filtering gives, after Fourier transformation, a single signal centered at 2.2 MHz, which is assigned to a ^2H nuclear Larmor frequency. ESEEM spectroscopy results strongly suggest that the unpaired electrons are located near Al and Si atoms of the zeolite framework and in the vicinity of H atoms of occluded BP. There is no experimental evidence to assign the trapped electron and the positive hole.

The experimental investigations on the presented system provide a reasonable picture of the electron-hole pairs that are stabilized indefinitely in the self-assembled array of $\text{BP}/\text{H}_n\text{ZSM-5}^{+/-}$. The biphenyl molecule lies in the ground state in the channel of the zeolite in close proximity to the Brønsted acid site. The electron and positive hole appear separated by

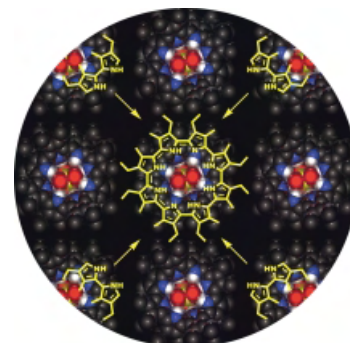
the occluded biphenyl molecule and efficiently trapped in the neighboring side pockets of the channel. The magnitude of the ferromagnetic exchange interaction appears to be related to the electronic structure of the path between the two paramagnetic centers.

Received: December 13, 2001
Revised: February 6, 2002 [Z18378]

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COVER PICTURE

The cover picture shows the simple, one-step synthesis of cyclo[8]pyrroles, a new class of aromatic heteroannulene. Using a newly developed biphasic oxidative coupling procedure that employs aqueous FeCl_3 as the oxidant, these novel porphyrin-like systems may be obtained in yields exceeding 70% starting from well-known bipyrrolic precursors. While formally derived from porphyrin as the result of substituting a pyrrole for each of the original bridging *meso*-carbon atoms, the cyclo[8]pyrroles differ from these quintessential tetrapyrrolic macrocycles by virtue of Q-like absorption bands that are red-shifted into the near IR. Cyclo[8]pyrroles also show a propensity for protonation and anion binding that is underscored by the X-ray structure of the sulfate salt that makes up the background for this illustration. More on these exciting new molecules can be found in the communication by J. L. Sessler et al. on pp. 1422–1425.

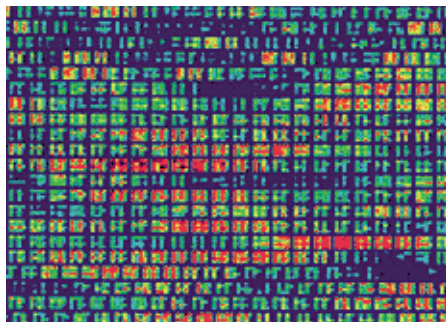


REVIEWS

Contents

Increasingly important elements of postgenomic biological research are DNA microarrays or DNA chips (see picture). Chemistry has made and should continue to make key contributions to the manufacture and application of these microarrays. This review covers current methods in DNA array production.

Angew. Chem. **2002**, *114*, 1326–1341

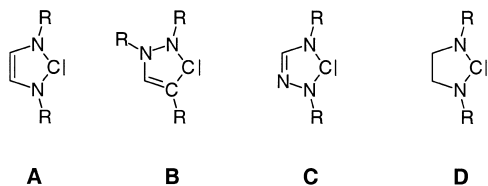


M. C. Pirrung* 1276–1289

How to Make a DNA Chip

Keywords: analytical methods •
combinatorial chemistry •
DNA microarrays • nucleotides •
surface analysis

Universal ligands: N-Heterocyclic carbenes such as **A–D** have become universal ligands in organometallic and inorganic coordination chemistry. C–H activation, C–C, C–H, C–O, and C–N bond formation are examples of catalytic processes, in which the established ligand class, the organophosphanes, will be supplemented and, in part, replaced by N-heterocyclic carbenes (especially of type **A**) in the new generation of organometallic catalysts to come.



Angew. Chem. **2002**, *114*, 1342–1363

W. A. Herrmann* 1290–1309

N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis

Keywords: carbene ligands • carbenes • heterocycles • homogeneous catalysis

Under the keywords flee, collaborate, and forget the effects of National Socialism on chemistry and biochemistry in universities and Kaiser Wilhelm Institutes are presented. At the center lies the dismissal and enforced emigration of all Jewish chemists and biochemists and a few of their non-Jewish colleagues, who were identified as critics of the regime or “Friends of Jews”, the different forms of collaboration of the remaining scientists, the isolated cases of nonconformity, and the general silence of German chemists after 1945—their effort to let the 12-year National Socialist rule and their share of the responsibility to be forgotten.

Angew. Chem. **2002**, *114*, 1364–1383

U. Deichmann* 1310–1328

Chemists and Biochemists during the National Socialist Era

Keywords: antisemitism • emigration • history of chemistry • science policy

MINIREVIEW

Perfectly branched: dendritic polymers have become increasingly important tools in medical diagnostics and therapy (see picture). In particular, progress has been made in diagnostics, especially in biosensors and by using dendrimers with Gd complexes in magnetic resonance imaging (MRI). Dendrimers also show promising therapeutic properties, with potential applications in gene transfection, in drug-delivery systems, and in neutron-capture therapy.



Angew. Chem. **2002**, *114*, 1385–1390

S.-E. Stiriba, H. Frey,*

R. Haag* 1329–1334

Dendritic Polymers in Biomedical Applications: From Potential to Clinical Use in Diagnostics and Therapy

Keywords: biosensors • dendritic polymers • gene transfection • medicinal chemistry • MRI

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>

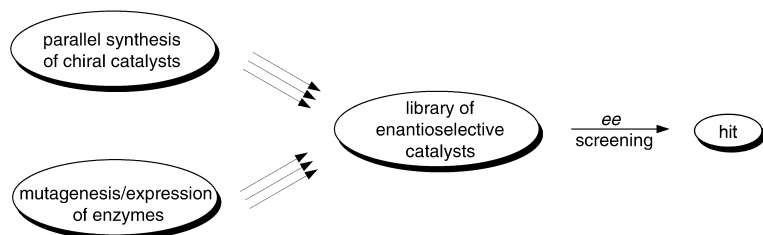
Cyclotetrasilene Ion: A Reversible Redox System of Cyclotetrasileny Cation, Radical, and Anion

T. Matsuno, M. Ichinohe,
A. Sekiguchi* ◆

Synthesis and Structure of Na₃N

D. Fischer, M. Jansen*

Combinatorial asymmetric catalysis and the directed evolution of enantioselective enzymes requires rapid high-throughput screening systems for assaying the *ee* value of large numbers of samples (see picture). Three new approaches are reviewed, which are based on DNA microarrays, enzymatic methods, and enzyme immunoassays.



Angew. Chem. **2002**, *114*, 1391–1394

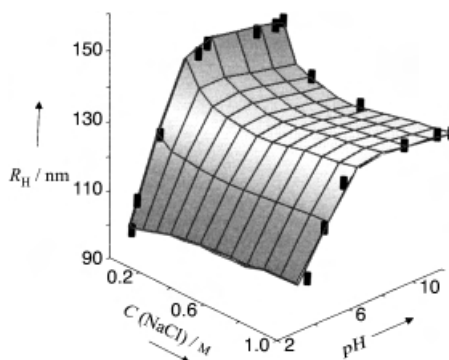
M. T. Reetz* 1335–1338

New Methods for the High-Throughput Screening of Enantioselective Catalysts and Biocatalysts

Keywords: asymmetric catalysis • combinatorial chemistry • DNA microarrays • enzyme immunoassay • high-throughput screening

COMMUNICATIONS

Polypeptide secondary structure controls the dimensions of aggregates formed from a polybutadiene-*b*-poly(L-glutamic acid) diblock copolymer after direct dissolution into water. The hydrodynamic radius (R_H) of these aggregates (even at high NaCl concentrations) were found to correlate (see picture) with a transition from a compactly folded α -helical poly(L-glutamic acid) block at low pH to an extended random coil conformation at basic pH.



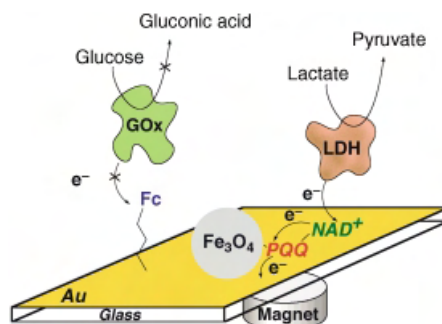
Angew. Chem. **2002**, *114*, 1395–1399

F. Chécot, S. Lecommandoux,*
Y. Gnanou, H.-A. Klok* 1339–1343

Water-Soluble Stimuli-Responsive Vesicles from Peptide-Based Diblock Copolymers

Keywords: amino acids • copolymers • nanostructures • self-assembly • vesicles

Sugar and magnetism: The selective analysis of glucose and lactate in a mixture was achieved by the application of glucose oxidase (GOx) and lactate dehydrogenase (LDH) using a ferrocene (Fc) monolayer-functionalized electrode, catalyst–NAD⁺-functionalized magnetic particles, and an external magnetic field (see schematic representation).



Angew. Chem. **2002**, *114*, 1399–1402

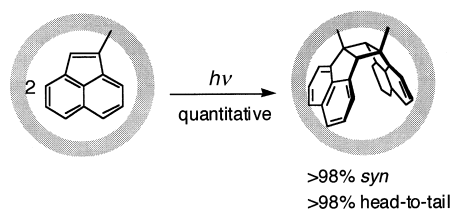
E. Katz, L. Sheeney-Haj-Ichia,
A. F. Bückmann, I. Willner* 1343–1346

Dual Biosensing by Magneto-Controlled Bioelectrocatalysis

Keywords: colloids • cyclic voltammetry • electrochemistry • magnetic particles • sensors



Molecular flasks of self-assembled M_6L_4 nanocages promote the [2+2] photodimerization of olefins in a surprisingly efficient fashion. Thus, the dimerization of acenaphthylenes and naphthoquinones quantitatively proceeded in the cavity with remarkable rate acceleration and perfect regio- and stereo-control (>98%, see scheme).



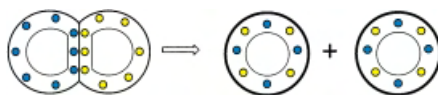
Angew. Chem. **2002**, *114*, 1403–1405

M. Yoshizawa, Y. Takeyama,
T. Kusakawa, M. Fujita* 1347–1349

Cavity-Directed, Highly Stereoselective [2+2] Photodimerization of Olefins within Self-Assembled Coordination Cages

Keywords: dimerization • palladium • photochemistry • regioselectivity • self-assembly

Stickiness of giant vesicles, visible under the light microscope, can be promoted or prevented (see figure) by substances such as poly-L-lysine (cationic), polyvinylpyrrolidone (nonionic; yellow), and heparin (anionic; blue). In one particular system, adhesion was time-dependent owing to exchange of components by a pair of electrostatically adhered vesicles.



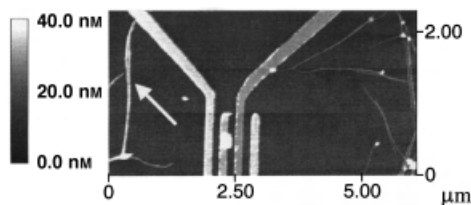
Angew. Chem. **2002**, *114*, 1406–1408

F. M. Menger,* V. A. Seredyuk,
A. A. Yaroslavov 1350–1352

Adhesive and Anti-Adhesive Agents in
Giant Vesicles

Keywords: adhesion • heparin •
membranes • vesicles

Combination of nanolithography and electrochemistry allows the chemical modification of individual single-walled carbon nanotubes (SWCNTs) by attachment of functional groups. This approach allows both the reductive as well as oxidative coupling of substituted phenyl groups, presumably to defect sites in the tubes. The thickness of the deposited layer can be controlled by the duration of the potential applied. The picture shows an atomic force micrograph of SWCNTs after the reductive coupling of a 4-nitrophenyl diazonium salt.



Angew. Chem. **2002**, *114*, 1409–1411

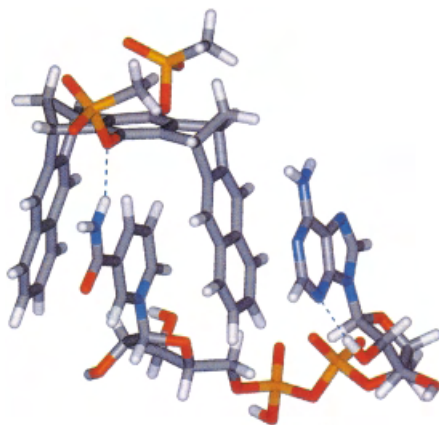
S. E. Kooi, U. Schlecht, M. Burghard,*
K. Kern 1353–1355

Electrochemical Modification of Single
Carbon Nanotubes

Keywords: electrochemistry •
nanotubes • oxidation • reduction •
surface chemistry



A molecular clip made of two naphthalene side walls and bisphosphonate arms selectively binds to *N*-alkylpyridinium ions in water. Through the unique potential of this clip to combine π -cation and electrostatic interactions with the hydrophobic effect, the host molecule is able to complex NAD^+ (nicotinamide adenine dinucleotide; see picture) efficiently in aqueous solution.



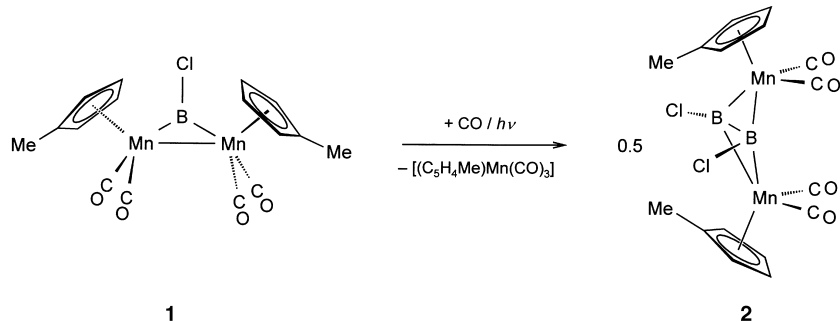
Angew. Chem. **2002**, *114*, 1411–1415

C. Jasper, T. Schrader,* J. Panitzky,
F.-G. Klärner* 1355–1358

Selective Complexation of
N-Alkylpyridinium Salts:
Recognition of NAD^+ in Water

Keywords: molecular clips • molecular
recognition • NAD • *N*-alkylpyridinium
salts • noncovalent interactions

Boron, butterflies, and the missing link: The first synthetic link between electron-precise borylene complexes such as **1** and electron-deficient metallaboranes is achieved with the preparation of **2**. This result introduces two novel features to the chemistry of the metallaboranes—unbridged B_2Hal_2 moieties (Hal = halogen) as cluster fragments and the four vertex *nido*-“butterfly” as a structural motif.



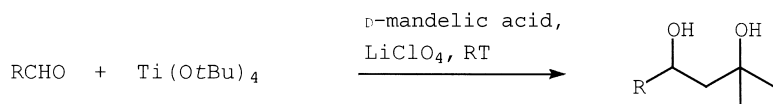
Angew. Chem. **2002**, *114*, 1415–1417

H. Braunschweig,* M. Colling, C. Hu,
K. Radacki 1359–1361

From Classical to Nonclassical Metal–
Boron Bonds: Synthesis of a Novel
Metallaborane

Keywords: boron • borylene complexes •
manganese • metallaboranes • metal–
boron bonds

Mobile hydrogen atoms: The hydrogen atoms of tertiary butyl groups are significantly more mobile than is generally assumed. Under very mild and acidic conditions aldehydes react with $\text{Ti}(\text{OtBu})_4$ to form diols in the presence of LiClO_4 and α -hydroxy acid (see scheme).



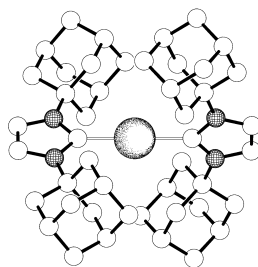
Angew. Chem. **2002**, *114*, 1423–1425

R. Mahrwald* 1361–1363

Enantioselective C–C Bond Formation with Titanium(IV) Alkoxides—an Unusual Alkylation

Keywords: aldehydes • alkylation • C–H activation • enantioselectivity • titanium

Highly active but sterically demanding: Ambient-temperature Suzuki cross-coupling of aryl chlorides is possible with a palladium(0) complex bearing two bulky, N-heterocyclic carbene ligands (see structure). Nearly quantitative yields are obtained within two hours with some reagents, which makes this compound the most active catalyst known to date under these conditions.



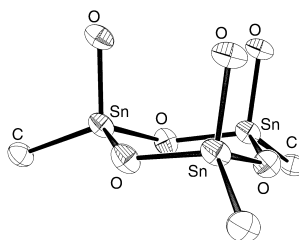
Angew. Chem. **2002**, *114*, 1421–1423

C. W. K. Gstöttmayr, V. P. W. Böhm, E. Herdtweck, M. Grosche, W. A. Herrmann* 1363–1365

A Defined N-Heterocyclic Carbene Complex for the Palladium-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides at Ambient Temperatures

Keywords: carbenes • carbene ligands • C–C coupling • homogeneous catalysis • palladium

An eighty-year-old question answered: The basic structural element of monoorganotin acids (see structure) is formed by *cyclo*-tristannoxanes in a chairlike conformation with ligands bonded to the Sn_3O_3 heterocycle in equatorial positions. The three axial hydroxy groups display a *cis* arrangement. Thus the fundamental structural element of this class of compounds is elucidated.



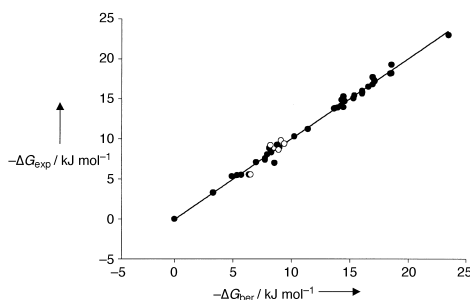
Angew. Chem. **2002**, *114*, 1425–1427

J. Janssen, J. Magull, H. W. Roesky* 1365–1367

X-Ray Structural Characterization of a Monoorganotin Acid

Keywords: chlorine • hydrolysis • monoorganotin acids • structure elucidation • tin

Energy increments for van der Waal effects are determined by bond-energy measurements on over 50 guest compounds (see diagram) and can be used for prediction. Hydrophobic effects can be discounted on the basis of comparison measurements with alkylated derivatives.



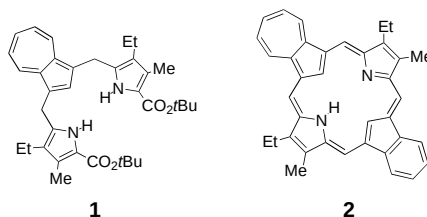
Angew. Chem. **2002**, *114*, 1418–1420

T. Liu, H.-J. Schneider* 1368–1370

Additivity and Quantification of Dispersive Interactions—from Cyclopropyl to Nitro Groups: Measurements on Porphyrin Derivatives

Keywords: bond energy • noncovalent interactions • porphyrinoids • solvent effects • supramolecular chemistry

A back-to-front synthesis of azuliporphyrins from an azulitripyrrane (**1**) has been developed. This methodology has allowed the first rational synthesis of the dicarbaporphyrinoid system **2**.



Angew. Chem. **2002**, *114*, 1429–1432

S. R. Graham, D. A. Colby, T. D. Lash* 1371–1374

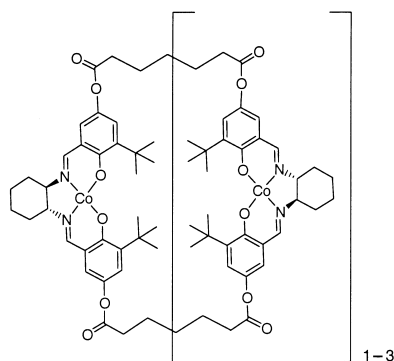
An Azulene Analogue of the Tripyrranes and Carbaporphyrinoids Therefrom

Keywords: aromaticity • azulene • nitrogen heterocycles • porphyrinoids



Prepared by a high yield, chromatography-free route, “oligosalen” exists as a mixture of dimer, trimer, and tetramer (see picture). Derived catalyst systems display remarkable activity and selectivity in the asymmetric ring-opening of epoxides, with turnover numbers exceeding 100 000 in some cases.

Angew. Chem. **2002**, *114*, 1432–1435



J. M. Ready, E. N. Jacobsen* 1374–1377

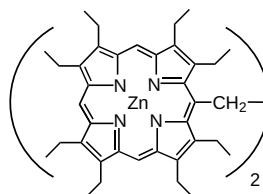
A Practical Oligomeric [(salen)Co] Catalyst for Asymmetric Epoxide Ring-Opening Reactions

Keywords: asymmetric catalysis • epoxides • homogeneous catalysis • kinetic resolution • N,O ligands



Supramolecular chirality induction and inversion processes can be controlled by phase transition. The achiral *syn* (face-to-face) conformer of the ethane-bridged bis(zinc octaethylporphyrin) (see figure) interacts with enantiopure monoamines in solution and solid-state phases to yield the corresponding *anti* conformer. The chirality sign in the solid state is opposite to that in solution because of the formation of an aggregated species with inverted intermolecular helicity.

Angew. Chem. **2002**, *114*, 1436–1439



V. V. Borovkov,* T. Harada, Y. Inoue, R. Kuroda* 1378–1381

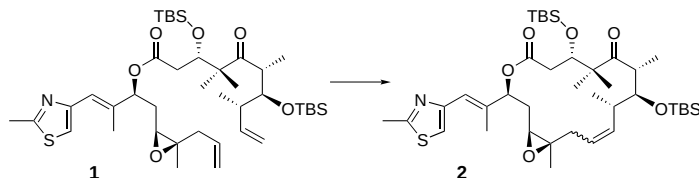
Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems

Keywords: chirality • circular dichroism • porphyrinoids • solid-state structures • supramolecular chemistry • zinc



A stereoselective synthesis of epothilone B was achieved by the metathesis of the diene **1**, by use of a new Grubbs catalyst to form the C9–C10 bond, followed by hydrogenation and deprotection of **2**; TBS = *tert*-butyldimethylsilyl.

Angew. Chem. **2002**, *114*, 1439–1441



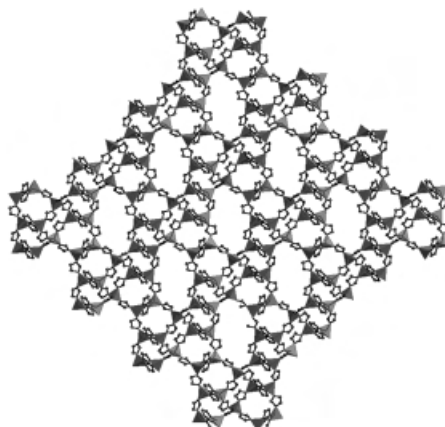
J. Sun, S. C. Sinha* 1381–1383

Stereoselective Total Synthesis of Epothilones by the Metathesis Approach Involving C9–C10 Bond Formation

Keywords: asymmetric catalysis • epothilones • metathesis • natural products • total synthesis

A highly robust metal-organic zeo-type was created by expansion of the zeolite topology. The novel nanoporous material $[\text{Co}_5(\text{im})_{10} \cdot 2\text{MB}]_{\infty}$ (see structure) exhibits not only a zeolite-like topology, but also the chemically functionalizable properties of zeolites; im = imidazole, MB = 3-methyl-1-butanol.

Angew. Chem. **2002**, *114*, 1442–1444

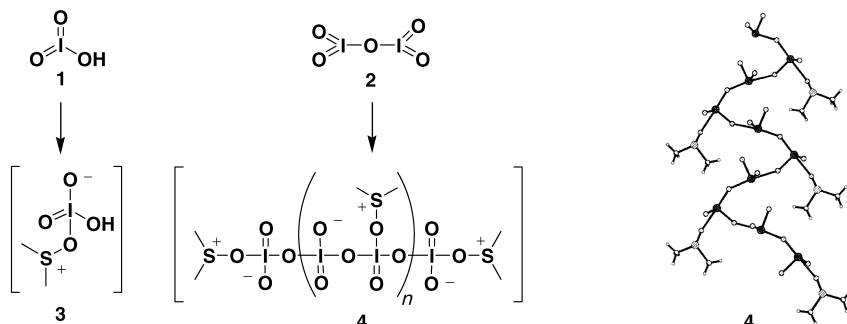


Y.-Q. Tian, C.-X. Cai, Y. Ji, X.-Z. You,* S.-M. Peng, G.-H. Lee 1384–1386

$[\text{Co}_5(\text{im})_{10} \cdot 2\text{MB}]_{\infty}$: A Metal-Organic Open-Framework with Zeolite-Like Topology

Keywords: cobalt • coordination polymer • crystal engineering • nitrogen heterocycles • zeolite analogues

Economic and convenient: Iodic acid (**1**) and iodine pentoxide (**2**) form complexes **3** and **4**, respectively, with DMSO when heated at 80°C for 1 h. The complexes are efficient agents for the dehydrogenation of ketones and aldehydes at 45–65°C. X-ray crystallographic analysis (see picture) shows that the iodine pentoxide · DMSO complex **4** self-assembles into a remarkable helix in the solid state.



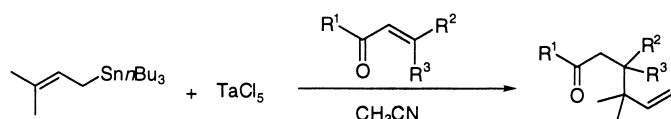
Angew. Chem. **2002**, *114*, 1444–1447

K. C. Nicolaou,* T. Montagnon,
P. S. Baran 1386–1389

HIO₃ and I₂O₅: Mild and Selective
Alternative Reagents to IBX for the
Dehydrogenation of Aldehydes and
Ketones

Keywords: dehydrogenation • enones •
hypervalent compounds • iodine •
synthetic methods

 **A superior method of conjugate allylation:** The transmetalation of allyltin compounds with TaCl₅ yielded active tantalum reagents for conjugate addition to enones. Even bulky allyl moieties could be introduced to enones in this manner (see scheme). Both cyclic and acyclic enones reacted readily under extremely mild conditions.



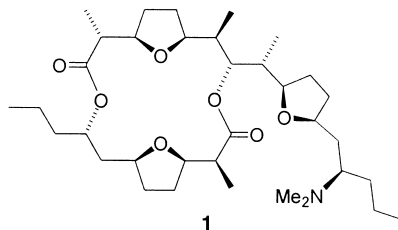
Angew. Chem. **2002**, *114*, 1447–1450

I. Shibata,* T. Kano, N. Kanazawa,
S. Fukuoka, A. Baba 1389–1392

Generation of Organotantalum Reagents
and Conjugate Addition to Enones

Keywords: allylation • Michael addition •
synthetic methods • tantalum • tin •
transmetalation

Complete stereoselectivity was observed in the total synthesis of pamamycin-607 (**1**), which proceeded by iodoetherification of γ -triethylsilyloxyalkenes in the presence of an essential additive, silver carbonate, to provide the requisite three *cis*-2,5-disubstituted tetrahydrofuran units. Other key functionalization includes cuprate addition to epoxide, olefinations, Paterson aldol condensation, Evans *anti* reduction, and macrolactonization.



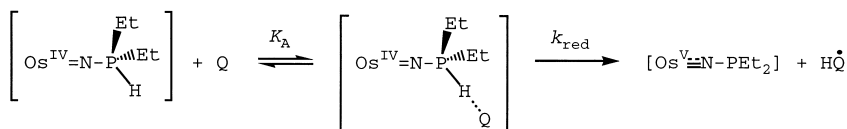
Angew. Chem. **2002**, *114*, 1450–1453

S. H. Kang,* J. W. Jeong, Y. S. Hwang,
S. B. Lee 1392–1395

Total Synthesis of (+)-Pamamycin-607

Keywords: asymmetric synthesis •
cyclization • natural products •
pamamycin • total synthesis

 **Remote from the metal:** The first example of proton-coupled electron transfer involving a phosphorus atom that is not directly bonded to a metal center (shown schematically; Q = benzoquinone) occurs with an osmium–phosphoraniminato complex. The large magnitude of the kinetic isotope effect is remarkable and opens the possibility of observing giant isotope effects in related reactions where proton-coupled electron transfer is the dominant mechanism.



Angew. Chem. **2002**, *114*, 1453–1456

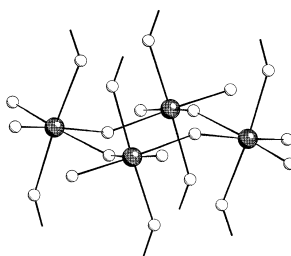
M. H. V. Huynh,*
T. J. Meyer* 1395–1398

Proton-Coupled Electron Transfer from
Phosphorus: A P–H/P–D Kinetic Isotope
Effect of 178

Keywords: electron transfer • isotope
effects • kinetics • osmium • P ligands •
reduction



Slow thermal decomposition of CrF_5 at 403 K affords a new crystal modification of CrF_4 . The basic units in the crystal structure of this $\beta\text{-CrF}_4$ are tetrameric rings formed by four corner-sharing CrF_6 octahedra (see picture), which are linked together to form isolated columns running along the c axis.



Angew. Chem. **2002**, *114*, 1456–1457

P. Benkič, Z. Mazej,*

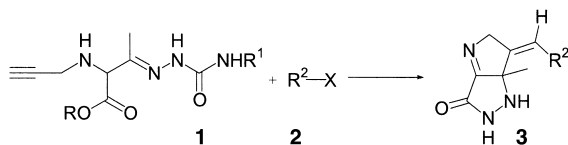
B. Žemva 1398–1399

A New Crystal Modification of Chromium Tetrafluoride: $\beta\text{-CrF}_4$

Keywords: chromium • fluorides • solid-state reactions • structure elucidation



Stereoselective dominos: Cascade reactions of easily accessible α -propargylamino-hydrazones **1** represent a simple and efficient method for the preparation of pyrazolones **3**.



Angew. Chem. **2002**, *114*, 1458–1460

E. Rossi,* A. Arcadi,* G. Abbiati,

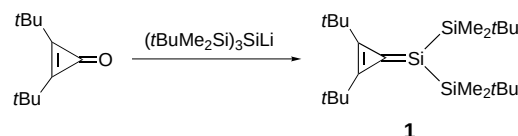
O. A. Attanasi,

L. De Crescentini 1400–1402

Sequential Base-Promoted Annulation/Palladium-Catalyzed Domino 1,5-Enyne Arylation and Vinylation of α -Propargylamino-hydrazones

Keywords: annulation • cyclization • domino reactions • nitrogen heterocycles • palladium

Unique structural characteristics and reactivities caused by the less-polar Si–C double bond in the 4-silatriafulvene **1** were revealed by spectroscopic studies and X-ray structural analysis. Compound **1** was isolated by applying a synthetic procedure using a sila-Peterson-type reaction.



Angew. Chem. **2002**, *114*, 1460–1462

K. Sakamoto,* J. Ogasawara, Y. Kon,

T. Sunagawa, C. Kabuto,

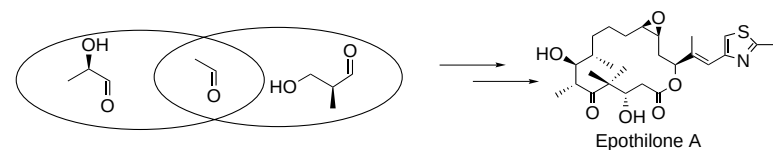
M. Kira * 1402–1404

The First Isolable 4-Silatriafulvene

Keywords: aromaticity • electronic structure • silene • silicon



Enzymatic reactions catalyzed by DERA provide the basis for a new strategy for the synthesis of novel pyranose synthons. The utility of this very convergent and effective method is demonstrated by the concise total synthesis of epothilones (see scheme; DERA = 2-deoxyribose-5-phosphate aldolase).



Angew. Chem. **2002**, *114*, 1462–1465

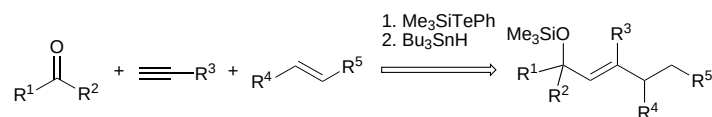
J. Liu, C.-H. Wong* 1404–1407

Aldolase-Catalyzed Asymmetric Synthesis of Novel Pyranose Synthons as a New Entry to Heterocycles and Epothilones

Keywords: aldol reaction • enzyme catalysis • epothilones • synthetic methods • total synthesis



The domino, sequential coupling reaction provides a convergent and stereoselective synthetic route for allylic alcohols from carbonyl compounds, alkynes, and alkenes (see scheme). The reaction involves sequential radical coupling reactions initiated by the α -siloxy radicals, which are generated from carbonyl compounds and silyl tellurides.



Angew. Chem. **2002**, *114*, 1465–1467

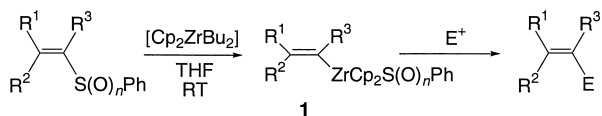
S. Yamago,* M. Miyoshi, H. Miyazoe,

J. Yoshida * 1407–1409

Convergent Synthesis of Silylated Allylic Alcohols by a Stereoselective Domino, Sequential Radical-Coupling Reaction

Keywords: C–C coupling • domino reactions • multicomponent reactions • radical reactions • synthetic methods

A transformation with promising versatility: The vinyl zirconium complex **1** can be prepared readily in situ from the educts mentioned in the title and reacts with electrophiles, including other transition metal complexes, to give polysubstituted olefins (see scheme; $n=0-2$, $\text{Cp}=\text{C}_5\text{H}_5$). A five-membered zirconacycle en route to the vinyl complex apparently isomerizes to give the stable *E* isomer before elimination.



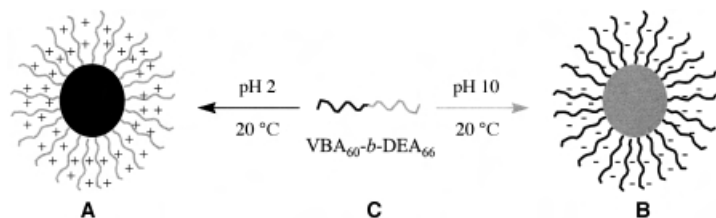
Angew. Chem. **2002**, *114*, 1468–1471

S. Farhat, I. Marek* 1410–1413

From Vinyl Sulfides, Sulfoxides, and Sulfones to Vinyl Transition Metal Complexes

Keywords: elimination • isomerization • sulfur • transmetalation • zirconium

Schizophrenic character: A novel zwitterionic AB diblock copolymer was prepared by atom-transfer radical polymerization (ATRP) of 2-(diethylamino)-ethyl methacrylate (DEA) and 4-vinyl benzoic acid (VBA). Both conventional micelles and inverted micelles can be formed in aqueous solution at ambient temperature, by controlling the solution pH. At low pH, VBA-core micelles (**A**) are formed, at high pH DEA-core micelles (**B**) are formed, and at neutral pH, the system precipitates (**C**; see figure).



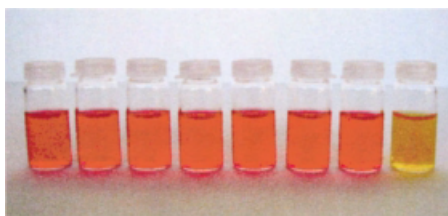
Angew. Chem. **2002**, *114*, 1471–1474

S. Liu, S. P. Armes* 1413–1416

Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer

Keywords: block copolymers • micelles • polymerization • self-assembly • surfactants

Nitrate sensing: A selective colorimetric sensing of nitrate by a mercury complex of an oxa-thia-aza macrocycle functionalized with an azo dye is described. The figure shows the color of acetonitrile solutions of the mercury complex in the presence of the following species: from left to right, no anion, F^- , Cl^- , Br^- , I^- , H_2PO_4^- , HSO_4^- , and NO_3^- .



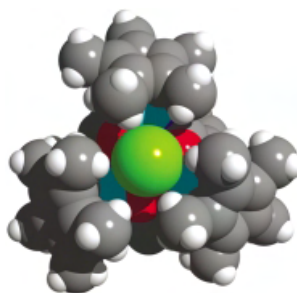
Angew. Chem. **2002**, *114*, 1474–1477

F. Sancenón, R. Martínez-Máñez,*
J. Soto 1416–1419

A Selective Chromogenic Reagent for Nitrate

Keywords: azo compounds • chromophores • mercury • nitrates • sensors

A redox-responsive receptor based on a self-assembled metallamacrocyclic is able to selectively bind molecular LiF (see X-ray crystal structure) and act as a highly selective chemosensor for the detection of fluoride anions by electrochemical means, even in protic solvents.



Angew. Chem. **2002**, *114*, 1477–1480

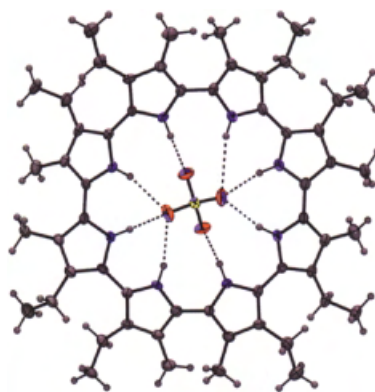
M.-L. Lehaire, R. Scopelliti,
H. Piotrowski, K. Severin* .. 1419–1422

Selective Recognition of Fluoride Anion Using a Li^+ –Metallacrown Complex

Keywords: fluorides • lithium • metallacycles • receptors • supramolecular chemistry

Easily obtained in a single step from bipyrrolic precursors in yields over 70%, cyclo[8]pyrroles represent a new class of porphyrin analogues that display the classic disklike structure of porphyrins. The X-ray crystal structure of one of the cyclo[8]pyrroles obtained (see picture) shows that the macrocycle acts as a formal diprotonated receptor and forms eight hydrogen bonds to a sulfate ion bound within its core.

Angew. Chem. **2002**, *114*, 1480–1483



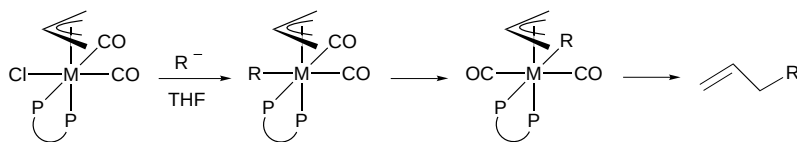
D. Seidel, V. Lynch,
J. L. Sessler* 1422–1425

Cyclo[8]pyrrole: A Simple-to-Make Expanded Porphyrin with No Meso Bridges

Keywords: anions • aromaticity • macrocycles • oxidative coupling • porphyrinoids



A cis-to-trans isomerization of the initially formed product is a key step following the nucleophilic attack of acetylide, alkyl, and enolate carbanions at the metal center of $[MCl(\eta^3-C_3H_5)(CO)_2(dmpm)]$ complexes ($M = Mo, W$; $dmpm = \text{bis}(\text{dimethylphosphanyl})\text{methane}$ ($P-P$); see scheme). Subsequent metal-to-allyl migration followed by elimination yields the corresponding coupling products.



Angew. Chem. **2002**, *114*, 1485–1487

J. Pérez,* V. Riera, A. Rodríguez,
S. García-Granda 1427–1429

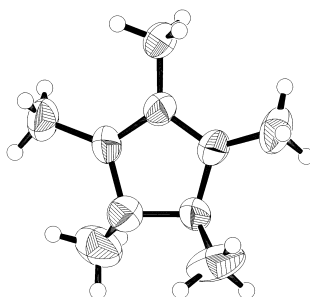
C–C Coupling between an η^3 -Allyl Ligand and Carbon Nucleophiles in Molybdenum and Tungsten Complexes: Structural Characterization of the Key Intermediate

Keywords: allylation • allylic compounds • molybdenum • tungsten



More than 100 years after the cyclopentadienyl anion appeared in the literature, the first cyclopentadienyl cation, the pentamethyl derivative $C_5Me_5^+$, has now been prepared in a single step as the tetrakis(pentafluorophenyl)borate salt. This material is crystalline and stable at room temperature for weeks. The crystal structure of $C_5Me_5^+$ (see picture) reveals localized bonding.

Angew. Chem. **2002**, *114*, 1487–1489



J. B. Lambert,* L. Lin,
V. Rassolov 1429–1431

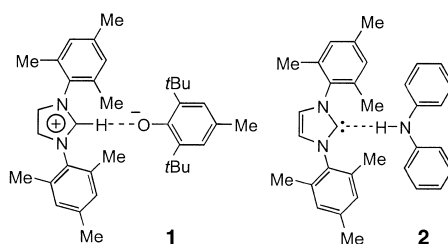
The Stable Pentamethylcyclopentadienyl Cation

Keywords: antiaromaticity • aromaticity • carbocations • structure elucidation



Two unprecedented hydrogen bonds were observed in the adducts obtained by the reactions of an N-heterocyclic carbene with a bulky phenol and with diphenylamine. In the former case, proton transfer yields an imidazolium aryloxide (**1**) containing the shortest C–H...O interaction seen to date and in the latter, the hydrogen atom remains bound to the organic acid but forms a unique N–H...C hydrogen bond (**2**).

Angew. Chem. **2002**, *114*, 1490–1492



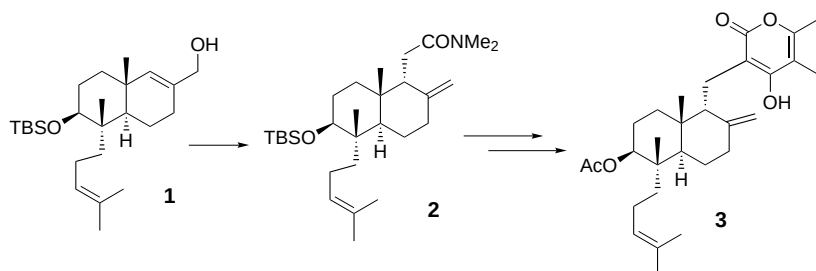
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S. P. Richards 1432–1434

On the Interaction between N-Heterocyclic Carbenes and Organic Acids: Structural Authentication of the First N–H...C Hydrogen Bond and Remarkably Short C–H...O Interactions

Keywords: carbenes • hydrogen bonds • pi interactions • structure elucidation



The key step in the total synthesis of sesquicillin (**3**) is a stereoselective Claisen rearrangement of **1** to afford **2**. The synthesis also features an efficient sequence to install an α -pyrone moiety in a hindered environment; TBS = *tert*-butyldimethylsilyl.



Angew. Chem. **2002**, *114*, 1492–1495



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Accelerated publications

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An Efficient Stereoselective Total
Synthesis of DL-Sesquicillin, a
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Keywords: aldol reaction • lactones •
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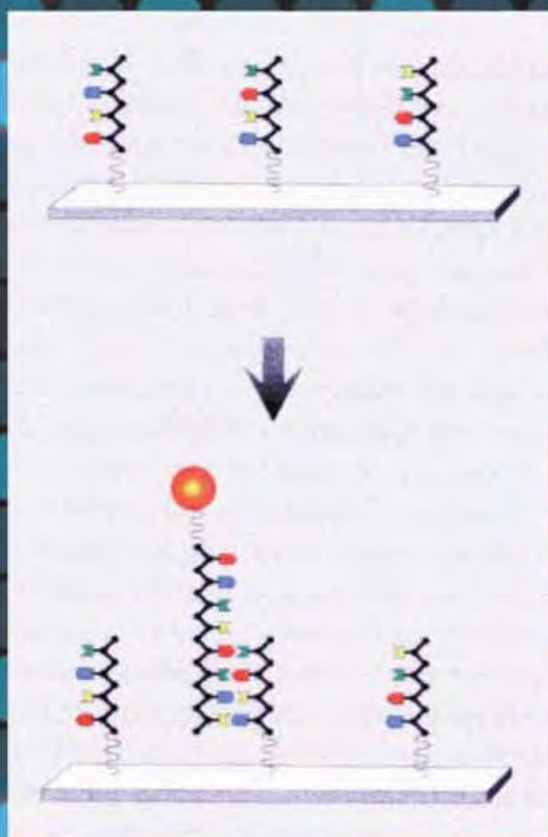
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The term DNA chip or DNA microarray refers to the systematic arrangement of biomolecular probes such as DNA molecules on a solid surface (e.g. glass, metal, or silicon wafer).



To identify a particular molecule, characteristic molecular interactions are made use of, for example, the sequence-specific hybridization of nucleic acids. After the hybridization of fluorophore-labeled cRNA or cDNA probes, the resulting hybridization pattern can be detected with a fluorescence scanner.

The middle part of the illustration was reproduced from the Review by C. M. Niemeyer and D. Blohm (ref.^[5] cited in this Review).

How to Make a DNA Chip

Michael C. Pirrung*

Microarrays are one of the hottest areas in biological research today. Microarrays have been mostly applied to nucleic acid analysis, specifically to the assessment of which genes are being expressed and at what level. Early microarrays were prepared by using photolithographic methods, which were more commonly used for integrated circuit ("computer chip") production. Hence the colloquial term "DNA chip" came into being. The completion of the sequencing of the human genome and that of many other organisms makes the determination of gene function an important next step in understanding the role of DNA in the

processes of life. DNA microarrays are an excellent tool to address this question because their numerous probe sites enable the analysis of many genes simultaneously. With good experience in this initial use, many further applications of microarrays are being developed, including genotyping in research and genetic diagnosis in medicine. DNA microarrays have made abundantly clear the power of vast parallelism in biological analysis, which is raising interest in other types of microarrays (small-molecule, protein). Many applications for DNA microarrays have been developed and clearly many more will emerge through the creativ-

ity of the scientists who use them. In early studies, users produced their own microarrays. The apparent power of microarrays has demanded improvements in production methods, and technologies from physical sciences and engineering are now being applied to DNA chips. Many branches of chemistry can contribute to improved methods: from synthetic chemistry (to attach or prepare DNA), to the physical chemistry of surfaces, to analytical chemistry (to assess surface reactions).

Keywords: analytical methods • combinatorial chemistry • microarrays • nucleotides • surface analysis

1. Introduction

Microarrays are defined here as monolithic, flat surfaces that bear multiple probe sites, often hundreds or thousands, and each bear a reagent whose molecular recognition of a complementary molecule can lead to a signal that is detected by an imaging technology, most often fluorescence. Literature references to microarrays before 1995 concerned arrays of electrodes rather than arrays of different molecules. The first molecular microarray, reported in 1991, was composed of peptides, not DNA, and was not even identified as a microarray.^[1] The photolithographic technology used to make that array was well discussed in an earlier review.^[2] Three books on DNA microarrays have been published,^[3] and the area has been reviewed recently,^[4,5] and discussed in the popular science press.^[6]

DNA arrays are topical owing to their promising ability for obtaining information on nucleic acid levels and sequences faster, simpler, and cheaper than traditional methods. Nucleic

acid recognition elements are readily synthesized and can often be reused. Major applications of DNA arrays are projected in large-scale genotyping and gene-expression profiling. Indeed, the parallel processing power of DNA arrays has encouraged a novel approach to science, born from genome sequencing: systematic investigation, in contrast to hypothesis-driven experimentation.

Two key parameters of a microarray are the number of different probe *sites* (spots) per unit area, which reflects its information density (also called complexity), and the number of probe *molecules* per unit area within an individual probe site (density, but often conflated in the literature with complexity). More probes per array means more information and a more powerful bioanalytical tool. To minimize array size, the probe sites (also called features) and their spacing (pitch) should be as small as possible, while still being able to detect reliably molecular recognition (Figure 1). Small arrays reduce the biological sample needed for analysis. A summary of such characteristics for a selection of chip production methods is provided in Table 1. The number of probe molecules in a given spot controls their intermolecular interactions, similar to the loading level on solid-phase synthesis supports. Close probe spacing enables complex interactions among multiple probes and analyte nucleic acids,

[*] Prof. M. C. Pirrung

Department of Chemistry, Levine Science Research Center
Box 90317, Duke University, Durham, NC 27708-0317 (USA)
Fax: (+1) 919-660-1591
E-mail: pirrung@chem.duke.edu

Table 1. Selected Parameters of DNA Chips.

Researcher	Affiliation	Density (molecules cm ⁻²)	Surface and Linking Chemistry	Representative Features
Schena ^[41]	Stanford U.	NR	glass-polylysine to PCR product	2479 × 345 μm
Belosludtsev ^[31]	Genometrix	3 × 10 ¹³	glass-silane-amine to native DNA	7 × ? μm
Beattie ^[20]	HARC	1.0 × 10 ¹²	silicon-glass-silane-epoxide to aminolink DNA	NR
Wöhrle ^[33]	U. Bremen	9.0 × 10 ¹²	glass-silane-amine-PDI-PAMAM-PDI to 5'-aminolink DNA	128 × 140 μm
Zammatteo ^[45]	U. Notre-D. de la Paix	3.6 × 10 ¹¹	glass-silane-aldehyde to 5'-aminolink DNA	9 × 0.4 mm
Boyce-Jacino ^[27]	Orchid	3 × 10 ¹³	glass-silane-thiol to disulfide DNA	49 × 1 mm
Steel ^[26]	Gene Logic	6 × 10 ¹²	microchannel glass-silane-thiol to maleimide-3'-aminolink-DNA	256 × 200 μm
Mirzabekov ^[34]	Argonne	1.8 × 10 ¹⁵	glass-polyacryl-hydrazide to 3'-dialdehyde-DNA	64 × 100 μm
Smith/Hamer ^[26]	U. Wisconsin	5.3 × 10 ¹²	silicon-undecanoate-polylysine-maleimide to 5'-thiol-DNA	2 × 2 mm
Hogan ^[21]	Baylor U.	1 × 10 ¹²	silicon-silane-epoxide to 5'-aminolink DNA	16 × ? μm
Téoule ^[39]	CIS Bio	1 × 10 ¹²	platinum to 5'-(poly)pyrrole DNA	4 × 0.62 mm
Heller ^[40]	Nanogen	1.6 × 10 ¹²	platinum-agarose-streptavidin to 5'-biotin DNA	10000 × 30 μm
Smith/Corn ^[19b]	U. Wisconsin	5 × 10 ¹²	gold-thiol-acid-polylysine-maleimide to thiol-DNA	8 × 3 mm
Corn ^[24]	U. Wisconsin	NR	gold-thiol/amine-maleimide to thiol-DNA	9 × 750 μm
Corn ^[25]	U. Wisconsin	1.5 × 10 ¹²	gold-thiol/amine-disulfide to thiol-DNA	16 × 500 μm
Yamamoto ^[37]	Canon	NR	quartz-silane-amine-maleimide to 5'-thiol DNA	64 × 70 μm
Pirrung ^[28]	Duke U.	NR	glass-silane-bromoacetamide to 5'-phosphorothioate DNA	64 × 100 μm
Zhao ^[29]	Amersham	NR	glass-silane-bromoacetamide to internal phosphorothioate DNA	100 × 150 μm
Southern ^[72]	U. Oxford	4 × 10 ¹³ (calc.)	in situ DMTr synthesis on glass - HEG linker	191 × 2.5 mm
Theriault ^[68]	Combion	1.2 × 10 ⁷	in situ DMTr synthesis	10000 × 0.1 mm
Brennan ^[67]	Protogene	1.3 × 10 ¹²	in situ DMTr synthesis on glass - HEG linker	? × 50 μm
Blanchard ^[69]	Rosetta	NR	in situ DMTr synthesis on glass - HEG linker	25000 × 100 μm
Trulson ^[7]	Affymetrix	1 × 10 ¹²	in situ photochemical synthesis on silica - HEG linker	135000 × 35 μm
McGall ^[60]	Affymetrix	NR	in situ DMTr/polymer film photoresist synthesis on silica - HEG linker	256 × 100 μm
Matson ^[71]	Beckman	1.2 × 10 ¹⁰	in situ synthesis on polypropylene - 5'-phosphoramidate linker	64 × 0.5 mm

NR - not reported.

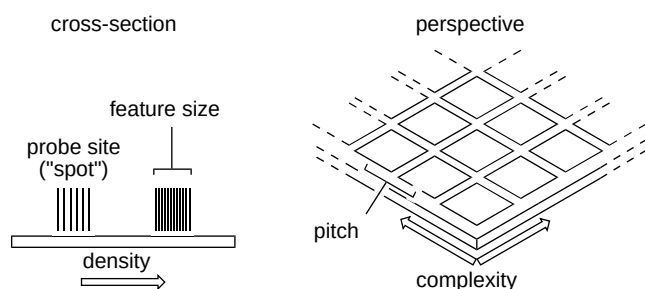


Figure 1. Key microarray parameters.

thus resulting in a nonclassical binding behavior, which can be advantageous.^[7] In other cases, a (mostly) normal Langmuir binding isotherm has been reported.^[8]

Although many chemical reactions have been developed for DNA attachment to flat surfaces, some have not been used

to form multielement microarrays. It seems evident that if one oligonucleotide can be prepared or attached, then, in principle, many can be. In practice, the repetitive steps required to generate highly complex microarrays means that small errors in individual steps accumulate to generate chaos. That the efficiency of a multistep sequence is the product of the yields of individual steps is familiar to chemists. Stamping techniques that may be excellent for creating patterned surfaces may be impractical to deliver ten or more reagents or thousands of DNA probes.

Many aspects of microarray production are common to the different techniques. One aspect is a linker required to create a distance between the surface and the section of oligonucleotide that is to be used in hybridization. This distance avoids steric clashes with incoming molecules and the whole operation more closely resembles conditions in solution. Ethylene glycol oligomers or simply a sequence of thymine



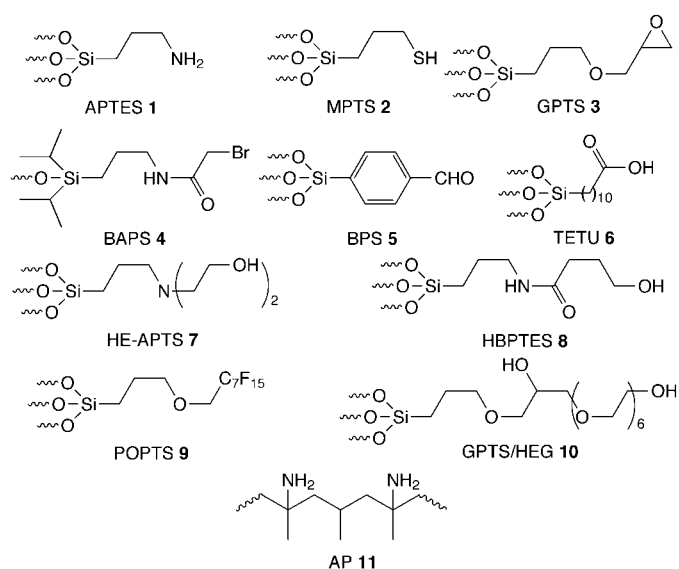
Michael Pirrung began his chemical career at the University of Texas at Austin. He completed his Ph.D. at the University of California at Berkeley with Clayton Heathcock, where his independent research initiated his interest in synthetic photochemistry. After one year at Columbia University, NY, with Gilbert Stork, he took up a position at Stanford. From 1988, he was a member of a group of scientists led by Alejandro Zaffaroni that formed a new company, Affymax, in Palo Alto. His work there focused on light-directed synthesis, which led to the first reported microarray in 1991. He is currently professor of chemistry at Duke University, where his research efforts lie in chemical biology, with an emphasis on microarray technologies and combinatorial chemistry.

(T) bases have been used as linkers. A wide number of protocols for slide preparation/derivatization have been reported. The existence of many solutions to a problem often means that none work very well. However, in an emerging field such as that of DNA chips, workers may not be aware of all contemporary research, and the value of particular technologies may not yet be widely known.

Much effort has been dedicated to the sourcing of the surface on which a microarray is made and its preparation. Owing to accessibility, the standard glass microscope slide has been most widely used, but more sophisticated surfaces, including fused silica, gold, and silicon wafers, are also used. Usually, a cleaning procedure is applied and can involve detergents, strong oxidizers ($\text{H}_2\text{SO}_4/\text{H}_2\text{O}_2$ or “piranha solution”, oxygen plasma, $\text{NH}_3/\text{H}_2\text{O}_2$), sonication, acid, or base. The purpose (or even success!) of cleaning is not always clear, although a generally accepted benefit is the removal of any organic surface contaminants that could interfere with subsequent silane-coating protocols.

For silicon oxide based surfaces, it is necessary to coat the chip with an organosilane. This silane should bear a functionality that can react with a group on the oligonucleotide or on a linker that is suitable for the synthesis of oligonucleotides. Thus, a knowledge of silicon coatings is very relevant to DNA chips. It is generally believed that the formation of siloxane thin films on silicon oxides involves alkoxy silane hydrolysis to a polymeric network that is physisorbed to silanol hydroxy groups in the coating stage. The generation of a stable chemisorbed film occurs upon annealing.^[9] Consistent slide derivatization with an organosilane has likely given many novice DNA chip workers significant difficulty. As a macroscopic process, coating is not readily monitored, although one consequence is usually a significant increase in hydrophobicity, which can be observed by the beading of water on the surface and analyzed through the contact angle. Such surfaces are often described as monolayers; *not* because of direct evidence but more likely because an idealized scheme for siloxane bonding does not permit multilayers. A report that oxidized silicon wafers can be coated with a common DNA chip derivatizing agent, APTES (**1**, Scheme 1), to form a true monolayer under very mild conditions (toluene, room temperature, 15 min) has been widely overlooked.^[10] Many investigators have used more forcing conditions for coating that can produce multilayers. Use of chemometric tools to optimize the coating of glass slides with MPTS (**2**, Scheme 1) showed that only the coating time and annealing step significantly affect ultimate thiol loading.^[11]

The design of the probe sequences that will be placed on a microarray seems straightforward—they must be complementary to the analyte. However, leveling the melting temperature of short probes with different G/C contents by changing their lengths may be necessary. Probes should also have minimal internal structure and should address sites in the analyte with minimal internal structure. These problems should be readily addressed by computation, although predicting the secondary structure of an RNA molecule is computationally intractable. An empirical heuristic that is based on hybridization to probe arrays can be used,^[12] and other guidelines have been advanced.^[13]



Scheme 1. Reagents for the derivatization of surfaces. APTES = amino-propyltriethoxysilane, MPTS = 3-mercaptopropyltrimethoxysilane, GPTS = glycidoxypentyltrimethoxysilane, HE-APTS = bis(hydroxyethyl)amino-propyltriethoxysilane, HBPTES = hydroxybutylamide propyltriethoxysilane, POPTS = (perfluorooctyloxy)propyltriethoxysilane.

2. Delivery of Presynthesized Oligonucleotides

Microarrays of presynthesized oligonucleotides have been widely produced. The factors that must be considered in their production include derivatization of the slides with functional groups, derivatization of the nucleic acid with complementary functional groups, delivery of tiny volumes of spotting solution, and deactivation of unreacted surface-bound functional groups. A quality issue is the distribution of oligonucleotide within each spot. A common observation is the formation of spots with greater oligonucleotide density at the edges than in the middle. Such a phenomenon is also observed when coffee is spilled and a ringlike stain is produced. This can be readily explained in terms of simple physics: solution flow to the spot edge with evaporation.^[14] This is one possible cause of anisotropic spots; contact-based printing methods might also damage the surface. To avoid this morphology, the wetting properties of the solvent must be modified, evaporation must be avoided, and/or surface damage must be limited in the spotting method.

Many new practitioners in this field, our research group included, likely have the initial rewarding experience of spotting a functionalized oligonucleotide onto a derivatized surface and detecting a nice bright spot, only to be chagrined to find that a control oligonucleotide without the functional group also gives a bright spot, either when a label is attached or in the subsequent hybridization. It is not surprising that native DNA can adhere strongly to glass surfaces; this is the basis of many kits used to purify plasmid DNA from minipreps. Indeed, it has been reported that derivatization of the oligonucleotide and the glass surface is unnecessary for assays, even under fairly stringent conditions.^[15]

The equipment for spotting oligonucleotides onto arrays were initially homemade, but are now commercially available.

The first such system was developed at Stanford University (see Section 2.2). Rose has provided an extensive analysis of the methods and equipment that can be used to deliver tiny volumes of oligonucleotide solution.^[16] Spotting can involve either bringing a pin or needle into contact with the surface or projecting a liquid droplet from a jet nozzle under pressure. The liquid volume that can be delivered is 50 pL–100 nL, and the resulting spot size is 75–500 μm . These two critical factors do not differ much between contact and noncontact methods, thus the choice of spotting technology must be based on other considerations. The design of “pins” for the delivery of pL volumes is ingenious (Figure 2). Many pins are essentially



Figure 2. Pin and stylus designs for the delivery of pL volumes.

highly miniaturized stainless-steel fountain-pen nibs with a gap that draws up the oligonucleotide solution by capillary action. These are commercially available^[17] in a wide range of dimensions and lead to a variety of spot sizes and densities. They can load up to $\sim 1 \mu\text{L}$ of solution so that multiple deliveries can be made from one loading. “Preprinting” several waste spots removes excess solution and enables consistent spotting. Other pins are solid, adhere solution to their faces (flat or concave), and deposit their entire load in one spot. In a modification of this concept, the solution is loaded into a metal ring through which a solid pin is pushed to first pick up and then deliver oligonucleotide, thus enabling multiple deliveries per load.^[18] Upon contact of either type of pin with the surface, a $\sim 1\text{-nL}$ spot is delivered, the diameter of which is determined by the surface energies of the pin, liquid, and slide. A universal concern when using delivery systems with multiple oligonucleotides is carryover between spotting a first oligonucleotide and returning to a source plate to pick up a second for spotting. Washing steps are required between samples. Multiple pins or jets in a printhead speed up array production, and up to 64 have been used. Automated spotting systems include fixed locations for the slides to be spotted and for the “source plates”, which are microtiter plates that contain the oligonucleotides. Both can be addressed by the printhead by means of a multiaxis positioning stage or gantry. The hydrophobicity of the silane film is useful to maintain (through surface tension) the spot size once it is delivered; the spot does not spread as it would on a hydrophilic surface. The environment must be controlled during deposition to maintain cleanliness and limit evaporation after spotting (relative humidity $>70\%$), so that oligonucleotide attachment, which can take hours with some methods, has sufficient time to occur. High humidity may also improve spot homogeneity.

2.1. Synthetic Oligonucleotides

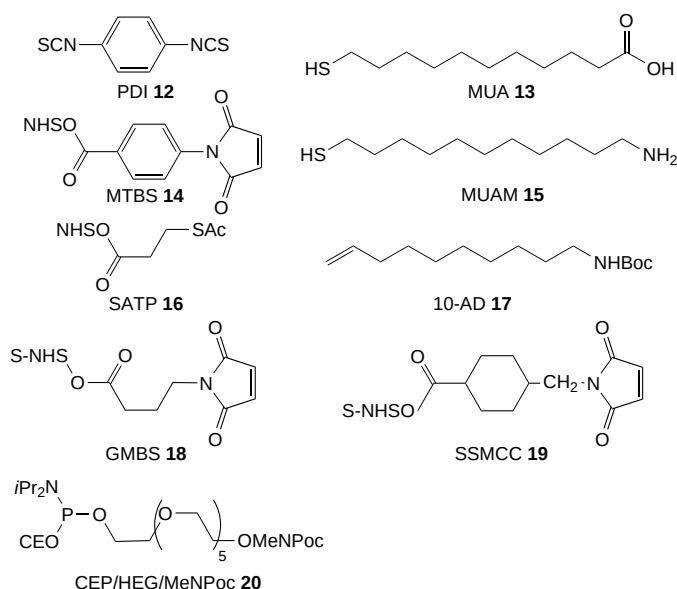
To immobilize synthetic oligonucleotides, chemical functionalities that can react with complementary functionalities

on the surface are introduced during conventional automated synthesis. Generally, linking units can be added at the 3' end (beginning of the synthesis), internal positions, or 5' end (end of the synthesis). For hybridization assays, the position of attachment should be irrelevant. For other assays in which enzymatic transformations (polymerase- or ligase-based^[19]) on the surface-bound oligonucleotide must occur, a free 3' end is required; thus the linkage must be internal or at the 5' end.

2.1.1. Spotting

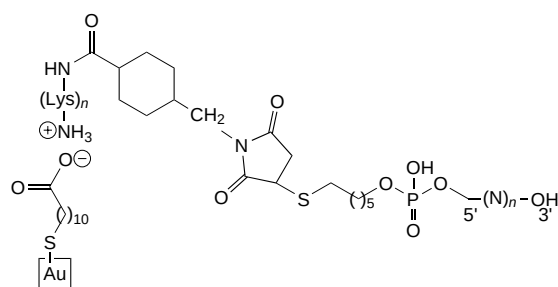
Early work on this production method came from Baylor University and Houston Advanced Research Center (HARC). Glass slides^[20] or SiO_2 -coated silicon wafers^[21] were treated with GPTS (**3**, Scheme 1) to introduce epoxide groups. Synthetic oligonucleotides (3'- or 5'-aminopropyl 9-mers and 36-mers, **21** and **22**, Scheme 6) were spotted in KOH (0.1M, 5 μL). The epoxide-opening reaction is facilitated at relatively alkaline pH values that maintain the amine as the free base, but is still relatively slow and inefficient ($\sim 1\%$). An increase in the number of triethyleneglycol phosphate spacer units between the DNA molecule and the surface attachment increases subsequent hybridization to long DNA targets, but has no effect with shorter targets.

DNA arrays also were prepared on glass by Corn and co-workers at the University of Wisconsin.^[22] Treatment of APTES slides with PDI (**12**, Scheme 2) enables the immobilization of 5'-amino oligonucleotides with a T_{10} spacer. About 20% of the deposited oligonucleotides are available for hybridization. A more sophisticated attachment chemistry was developed based on self-assembled monolayers (SAMs) of thiols on gold. A multilayer structure was created, starting with MUA (**13**, Scheme 2), which adsorbs polylysine electro-



Scheme 2. Linking reagents for DNA attachment. S-NHS = sulfo-succinimidyl, Boc = *tert*-butoxycarbonyl, MeNPoc = ((α -methyl-2-nitropiperonyl)-oxy)carbonyl, PDI = 1,4-phenylenediisocyanate, MUA = 11-sulfanylundecanoic acid, 11-MUAM = mercaptoundecylamine, 10-AD = 10-amino-1-decene.

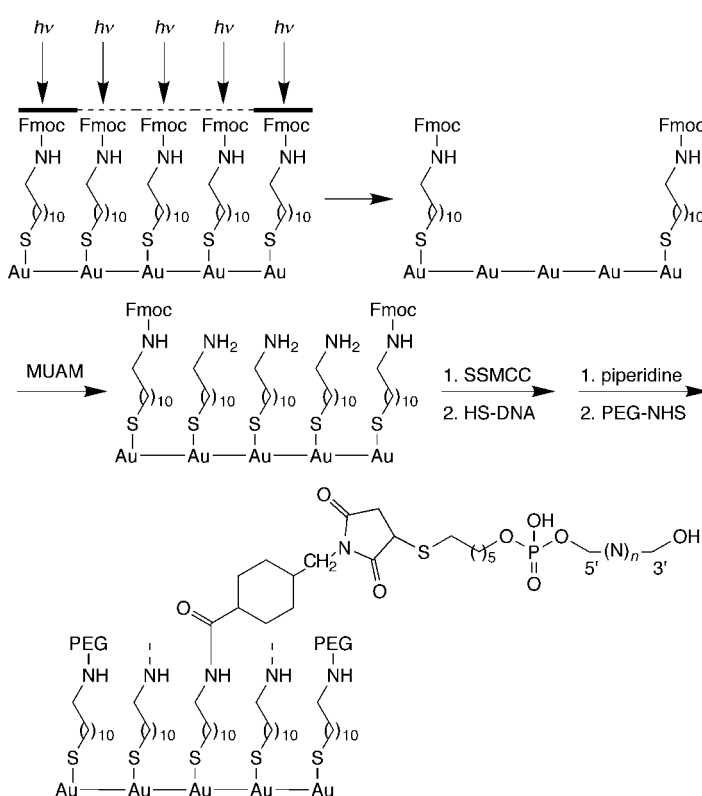
statically (Scheme 3).^[23] This surface is derivatized with the cross-linking agent SSMCC (**19**, Scheme 2), which enables it to react with oligonucleotides that are modified at the 5' end. The delivery of 0.8- μ L drops results in 3-mm spots. The gold substrate allows analysis by means of surface plasmon resonance (SPR), thus permitting the direct observation of each production step (based on measurements of film thickness) as well as binding events. SPR imaging^[8] offers an alternative to confocal fluorescence microscopy, thus far the workhorse of the array field.



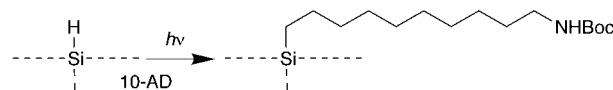
Scheme 3. Thiol/gold multi-layer DNA array.

Corn and co-workers also developed a similar method to generate a prepatterned array whose feature size is not limited by spreading (Scheme 4).^[24] A first layer of 11-MUAM (**15**, Scheme 2) was protected with Fmoc. Photolithography (750- μ m features) removed thiols from exposed areas of the gold by oxidation, thus creating array elements that were again exposed to MUAM to form areas of amine surface surrounded by hydrophobic Fmoc amine groups ("streets" or nonwetting regions). These array elements were derivatized with SSMCC (**19**; delivery of 0.1 μ L by micropipette) followed by an oligonucleotide 5' thiol. The Fmoc groups were removed, and the resulting amines were treated with a polyethylene glycol NHS ester to render the streets resistant to adsorption. This method (Scheme 4) is more complex than the direct modification of gold surfaces with thiolated DNA sequences, but decreases the amount of nonspecific DNA attachment and permits the density of surface-bound DNA to be varied by dilution with simple thiols. A further extension of this chemistry is the formation of disulfide surfaces for attachment to thiol-derivatized DNA (**23**, Scheme 6).^[25] The patterned MUA surfaces are treated with SATP (**16**, Scheme 2), which is deacetylated to give a thiol. The thiol is converted with (PyrS)₂ into a disulfide that reacts with 5'-thiol-DNA. All these surfaces were extensively characterized by using IR spectroscopy and SPR imaging.

Novel methods for the modification of silicon surfaces for DNA attachment were also investigated at the University of Wisconsin (Scheme 5).^[26] Silicon with terminal hydrogen atoms is prepared by treatment of oxidized silicon wafers with HF. The Si-H bond undergoes a photochemical addition to alkenes to form a Si-C bond. When this method is applied to Boc-protected 10-AD (**17**, Scheme 2) a Boc amine surface is produced. Deprotection permits coupling with SSMCC for attachment of thiolated DNA, as described before. The amine



Scheme 4. Thiol/gold predefined DNA array. Fmoc = 9-fluorenylmethoxycarbonyl, PEG = polyethyleneglycol, NHS = hydroxysuccinimide.

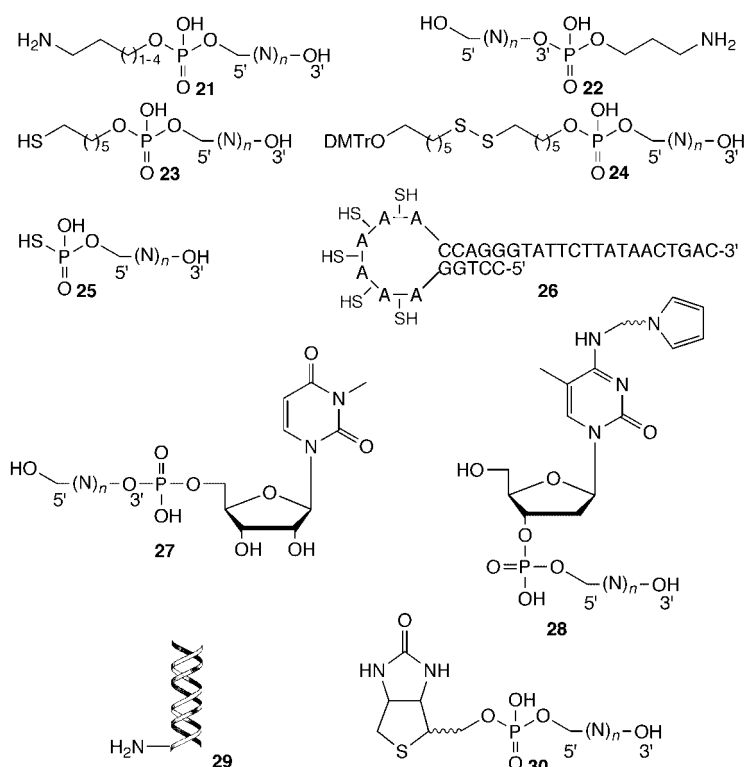


Scheme 5. Si/C DNA array attachment.

sites can be diluted by including dodecene in the initial surface functionalization. These surfaces have been well characterized by X-ray photoelectron spectroscopy.

Researchers at Orchid developed the immobilization of disulfide-modified oligonucleotides on sulfanylsilane-derivatized glass by thiol-disulfide exchange.^[27] Slide coating is performed in a solution of MPTS in ethanol/acetic acid, followed by annealing. Oligonucleotides **24** derivatized with a 5'-disulfide modifier (Scheme 6) are deposited in carbonate buffer. The efficiency of attachment is directly related to oligonucleotide concentration up to 20 μ M, when it becomes saturated; the half-time for attachment is approximately 10 min. Hybridization solutions do not damage the disulfide linkage, and approximately 16% of the deposited oligonucleotides are available for hybridization. This method was used to generate arrays with a syringe robot and the MicroFab jet (Section 3.1.2), which produced 140- μ m spots.

Difficulties with the reproducibility of silane coatings were addressed by our group^[28] by using a strategy drawn from chromatography, in which silanes that bear only one alkoxy group give superior sorbents because they cannot form siloxane polymers. However, simple monoalkoxysilane surfaces are also more labile than trialkoxysilanes to a nucleophilic attack at silicon that removes the silane from the surface. Two strategies address this problem: introduction of bulky groups



Scheme 6. Functionalization of oligonucleotides for coupling with the slide. DMTr = dimethoxytrityl.

at the silicon atom (e.g. BAPS, **4**) and mild DNA attachment conditions based on the known reaction of bromoacetamides with 5'-phosphorothioate DNA. Researchers at Amersham extended this method by incorporating phosphorothioates into internal positions of an oligonucleotide hairpin **26** (Scheme 6) that could prime a DNA polymerase extension.^[29]

The noncovalent interactions of positively charged polylysine surfaces with negatively charged polymerase chain reaction (PCR) products are adequate to immobilize them as probes (see Section 3.2). It is therefore logical that the charge of shorter oligonucleotides might also be adequate for immobilization. This offers the advantage that no chemical modification of the synthetic probe is required. Operon uses polylysine slides to immobilize synthetic 70-mers by essentially the same methods reported by the Stanford University groups.^[30] Genometrix makes use of APTES slides to immobilize dodecamers.^[31] After drying, the amines are capped, first with acetic anhydride and then with succinic anhydride to produce a slightly anionic surface that exhibits low nonspecific adsorption of analyte DNA. The high initial affinity of the positively charged surface for probe DNA and the engineered reduced affinity for target DNA through acylation is an essential feature of microarray methods based on aminated surfaces.

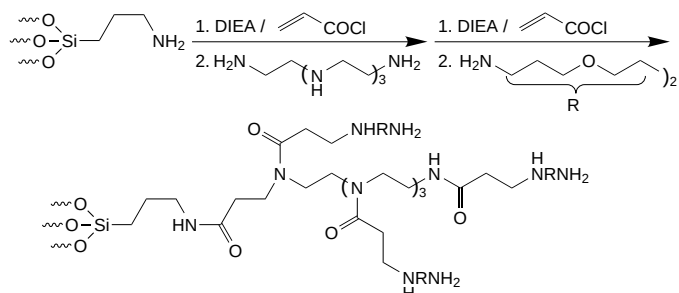
An increase in oligonucleotide density within probe sites should increase signals and therefore sensitivity. A versatile dendrimeric linker for oligonucleotide attachment was developed for this purpose at the German Cancer Research Center, Heidelberg (Germany).^[32] Aminated glass or polypropylene surfaces were subjected to a four-step divergent dendrimer synthesis (Scheme 7) that resulted in a fivefold increase in the

primary amine loading. The amines were activated by means of the diisothiocyanate method for the immobilization of 5'-aminolink probes or PCR products (see Section 3.2) in volumes of 1–50 nL to create 0.2–0.8-mm spots. The residual isothiocyanate groups were deactivated with 6-aminohexanol.

An alternative method involves the attachment of a preformed dendrimer to the surface.^[33] Workers at the University of Bremen bound PAMAM dendrimers to an isothiocyanate-activated aminated glass surface, then further activated the amine groups with PDI for the binding of a capture oligonucleotide (in 1 nL or less). The hybridization signal from these arrays was twice as strong as that from conventional aminosilane glass, and was more uniform and reproducible.

The density of sites on a functionalized surface should be directly proportional to surface area. A flat, nonporous glass/silicon surface must have a surface area close to the macroscopic surface area of the object. The formation of a three-dimensional structure on the surface should increase the area and therefore the oligonucleotide density. Two approaches to this goal have been taken.

Drawing on gel-making methods widely used in molecular biology, workers at Argonne National Lab polymerize acrylamide/bis-acrylamide into predefined 10–100- μ m square pads by using photolithography (Figure 3).^[34] The resulting 5–20- μ m thick



Scheme 7. In situ synthesis of a dendrimeric linker. DIEA = diisopropylethylamine.

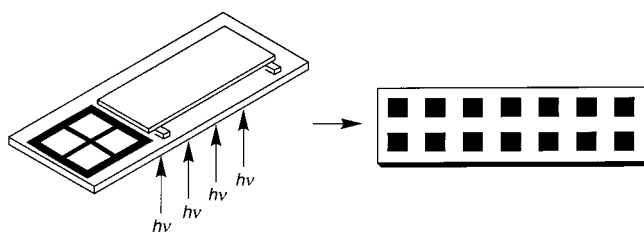


Figure 3. Production of a gel-pad array.

polyacrylamide pads have pL to nL volumes and are separated by 20–200- μ m hydrophobic streets. Amine immobilization sites are added to the gel pads by transamidation with diamines. Because the 4% cross-linking limits the porosity of the gel, a limit of 150–200 nt is imposed on the DNA to be immobilized. Aldehydes are introduced into this DNA by synthesis with a 3-methyluridine at the 3' end (e.g. **27**,

Scheme 6), which can be cleaved with periodic acid. Functionalized oligonucleotide solutions are delivered to the gel-pad array with a pin or a piezoelectric capillary jet.^[35] The dialdehyde is irreversibly attached to the gel by reductive amination (pyridine · BH₃).

Workers at Gene Logic have developed three-dimensional “flow-thru” chips that theoretically increase the surface area 100-fold over that of planar substrates.^[36] Commercially available glass array plates (48 × 48 mm²) with 10-μm hexagonal-packed microchannels provide the starting point. Whereas the channels are readily filled with liquid by capillary action, exchange with liquids outside is very slow. Pressure or ultrasonication are used to force liquid through the microchannels, which are emptied by wicking. Silanization with a solution of MPTS (**2**, Scheme 1) gives a thiol surface. Amino-link oligonucleotides that are modified with the maleimide cross-linking agent GMBS (**18**, Scheme 2) are deposited in volumes of 5–10 nL with a piezoelectric capillary jet^[35] because glass array plates cannot tolerate contact printing methods. The resulting spots (~200 μm) are about 60 % of the size of those obtained with planar chips and do not exhibit the “coffee-ring” effect. The functionalization level reported for these chips is comparable to that for planar surfaces, thus their three-dimensional structure offers no advantage in increasing the total amount of immobilized oligonucleotide. They also have a somewhat higher fluorescence background than slides, but still give a 44-fold enhancement of the hybridization signal over that of planar chips. This enhancement was attributed to a larger surface area per probe site, which means a lower density of probes with equivalent probe loading.

2.1.2. Jets

The delivery of reagents for microarray production by means of jets has been reported by several groups. Contrary to the case in spotting methods, no direct contact is made with the surface. Bubble jets are simple semiconductor devices developed for printers; fluid is ejected from a nozzle by rapid heating. Researchers at Canon have reported DNA ejection in a solvent that includes glycerin, urea, and thiodiglycol as wetting agents.^[37] Thermal and shearing stresses of the bubble jet do not damage DNA of 10–300 nt. Up to 12 different oligonucleotide solutions could be dispensed in volumes of 24 pL, and 70-μm spots were created. Ejected 18-mer 5' thiol oligonucleotides were immobilized on maleimide-modified aminated glass slides.

A drop-on-demand jet system with ten independent fluid channels in an integrated piezoelectric block printhead (see Section 3.2) was developed by researchers at MicroFab.^[38] Jet openings are 40 μm in diameter and 2 mm apart and deliver oligonucleotides in 20 % aqueous ethylene glycol. The printhead must be brought to within 200 μm of a GPTS-derivatized slide for printing.

2.1.3. Other Methods

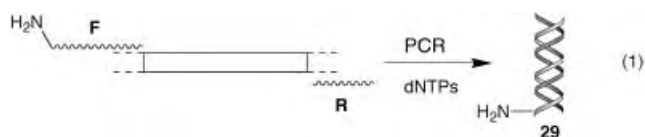
CIS Bio have reported the electropolymerization of oligonucleotides directly onto platinum minielectrodes.^[39] The oligonucleotides are synthesized with a 5-methylcytidine

moiety at the 5' end; a pyrrole group is linked to N4 (**28**, Scheme 6). Oxidation by repeated potential sweeping in the presence of approximately 10000-fold excess pyrrole produces a 50-nm layer of polypyrrole, with fractional incorporation of oligonucleotide-bearing pyrrole groups.

Nanogen brings an additional variable, electric field, into the parameters that can be manipulated in microarray production and use.^[40] This method is conceptually similar to electrophoresis, except that molecules move freely in solution. It relies on an array of as many as 10000 platinum microelectrodes, each as small as 25 μm, on a silicon wafer substrate produced by common techniques for semiconductors. The electrodes are coated with a 1–10-μm permeation layer of streptavidin–agarose that serves to insulate the DNA from deleterious electrode reactions and to immobilize biotin-derivatized 12- to 26-mer oligonucleotide probes **30** (Scheme 6) that are concentrated at the electrode pad by a positive electric field. The movement of DNA in the field requires a low conductivity buffer such as histidine. For simple 5 × 5 and 10 × 10 arrays, external electrical connections can be made directly to each electrode. For more complex arrays, the array may have onboard CMOS-FET (complementary metal oxide semiconductor-field effect transistor) logic to control each electrode so that the number of external connections is minimized. The active area of the array is 2–4 mm². The ability to control the field at the electrode-immobilized probe enables analyte to be brought to the electrode from dilute solution and adds an additional type of control, “electronic stringency”, during the hybridization step.

2.2. Biologically-Derived Nucleic Acids

Many biological studies into microarrays have as their starting point a set of clones whose functions and sequences may be unknown. Thus, the probe array is not designed based on a sequence, but the clones themselves are converted into probes that can be used to detect cellular RNA. Generally, this is accomplished by PCR. PCR not only allows the production of quantities of a particular nucleic acid by amplification, but also enables specific reactive chemical groups or labels to be introduced during the PCR [Eq. (1)] because all product molecules **29** are derived either from the



primers or from deoxynucleotide triphosphates (Scheme 6). These microarray production technologies are the most widely used in biology laboratories today and have created a demand for supplies that is now commercially available.

Two groups at Stanford University made the first widespread use of DNA chips in studying gene expression.^[41] The protocols for chip production have been extensively described

and widely adopted and adapted. Slides coated with polylysine provide a good starting point for this technology and are commercially available. Spotted probe DNA adheres to this surface through, at least initially, electrostatic interactions, and hybridization with analyte DNA does not disrupt this adhesion. A stylus (Figure 2) is used to deposit 5 nL of a PCR product (>1 kb) and gives spots of <350 μm . The addition of 1.5 M betaine in the spotting buffer improves spot homogeneity (no “coffee ring”), increases spot viscosity, slows spot evaporation without affecting the surface tension needed to keep it from spreading, and results in a 2.5-fold increase in the signal.^[42] The stylus moves on a gantry over an X,Y table. After hydration in a humid environment, the spots are quickly dried. The spotted DNA can also be photochemically cross-linked to the surface. This process has a long history in the manipulation of DNA on membranes; attachment may be based on nucleophilic substitution of the lysine amine group on T.^[43] Residual amine groups on the polylysine are capped with succinic anhydride in borate buffer or in an organic solvent^[42] that prevents the spreading of spotted DNA on the slide as is sometimes seen in aqueous solvents. To prepare probes for hybridization, the array is heated to denature the double-stranded PCR product.

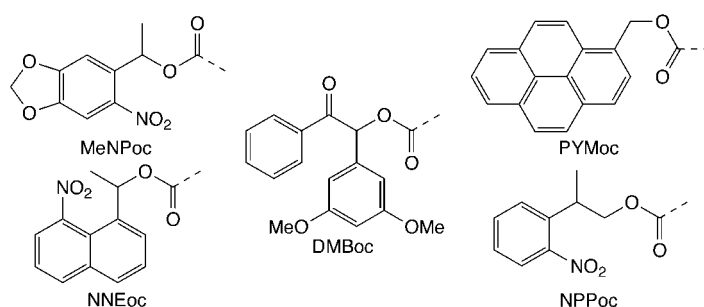
An alternative covalent linking chemistry has also been introduced by the groups at Stanford University. PCR products from primers that bear 5'-aminolink groups (**29**, Scheme 6) enable the use of another commercially available slide coated with a silane aldehyde **5** (Scheme 1). After 1056 PCR products were spotted as described above, the array was incubated with NaBH_4 for 5 min to reduce the imine group.^[44] The attraction of this protocol is a tenfold increase in sensitivity as a result of reduced background fluorescence, thus enabling the detection of mRNA that represents 1/500 000 of the total mRNA in a sample. One disadvantage of aldehyde slides is that they can oxidize in air to the acid. Other workers have shown that 5'-aminated PCR products (1-nL drops give 400- μm spots with a 1000- μm pitch) can also be coupled to carboxylic acid coated glass (TETU, **6**, Scheme 1) with carbodiimides.^[45]

Electrostatic binding of PCR products to APTES slides in the presence of sodium thiocyanate (3–5 M) has been reported by researchers at Molecular Dynamics.^[46] Despite the fact that no further treatment or capping is used, a significant fraction of the deposited DNA is retained during hybridization and wash steps. Their Gen III spotter deposits nanoliter volumes of DNA from 12 matched pens created from stainless steel capillaries with a slot cut in one wall (Figure 2).

3. Synthesis In Situ

An earlier review on spatially addressable combinatorial chemistry encompasses synthetic methods for preparation of DNA chips in situ.^[2] A major attraction of in situ synthesis is that it is a combinatorial method that enables the preparation of many more compounds than the number of chemical steps. However, serial methods of synthesis that proceed very rapidly have advanced with the benefit of engineering

technology to the stage that they may be time-competitive with some parallel-synthesis methods. Two strategies exist for the in situ synthesis of oligonucleotides. Each synthesis cycle has two stages, the deprotection step and the coupling step, and either can be spatially directed to the individual probe sites, while the other step can be performed at all sites simultaneously. An important consideration is the direction of DNA synthesis, because some assays require DNA with free 3' ends (see Section 2.1). In the case of the deposited arrays described above, locating the attachment anywhere other than at the 3' end is readily accomplished by automated synthesis. Conventional DNA synthesis proceeds from 3' $\rightarrow$ 5', thus the DNA is attached at its 3' end for arrays synthesized in situ. Amidites with reversed orientation (5'-phosphoramidite, 3'-dimethoxytrityl) are commercially available and can be used in the jet and in physical masking methods. However, they must be prepared with appropriate photochemically removable groups for photolithographic synthesis (Scheme 8). It is also conceivable to synthesize the DNA normally and then to reverse the attachment, but this has thus far only been reported on bead supports.^[47] The direction of synthesis can be a vital issue, as it has been shown that hybridization assays with the GeneChip (see Section 3.1) cannot detect insertion and deletion mutations in the p53 tumor suppressor gene,^[48] whereas primer extension assays readily do.^[49]



Scheme 8. Photochemically removable protecting groups for the synthesis of DNA microarrays.

3.1. Photolithography

The Affymetrix method of microarray production is by now a very familiar process. A surface is coated with linker molecules that bear photoremovable protecting groups. The pattern of irradiation (dictated by masks) deprotects certain regions, which are coupled to monomer units that are exposed to the whole surface. The process is repeated to build up different sequences at different sites. The combinatorial synthesis enables 4^l different sequences of length l to be prepared in $4 \times l$ chemical steps. This method was described, primarily for peptide synthesis, in an earlier review,^[2] and a good summary of its application to DNA chips is available.^[50]

The first report by the research group at Affymetrix on the application of this technology to DNA array production introduced the MeNPoc photoremovable protecting group (Scheme 8) in the preparation of DNA probe sequences

(>200).^[51] The protecting groups for the nucleobases are phenoxyacetyl (Pac) for A and isobutyryl for G and C, the so-called “easy-off” groups^[52] that can be removed with ethylenediamine or ethanolamine in ethanol in 4 h at room temperature. The HE-APTS (7, Scheme 1) surface is prepared for synthesis by treatment with **20** (Scheme 2).

Subsequent work at Affymetrix^[53] made use of fluorescein derivatization and imaging to determine the number of 5' hydroxy groups produced in each step. This showed that the photochemical deprotection reaction is strictly first order and gave half-times of 9–13 s at 27.5 mW cm⁻² for each monomer unit. The influence of the solvent on the rate of surface photodeprotection was studied, and a nonpolar solvent or no solvent proved best. Whereas some previous users of nitrobenzyl photochemistry have included reagents to scavenge nitrosoaldehyde by-products, this does not seem necessary with the MeNPoc group. The average yield of a MeNPoc-based DNA synthesis cycle (91–98 %) was measured by using a similar fluorescence-staining technique. The basis of the low cycle yields on microarrays is unclear, as solution-based photochemical deprotection and coupling proceed in very high yields. Low cycle yields mean that the purity of these sequences synthesized in situ is fairly low, but the number of full-length, accurate probes is still significant and evidently adequate for use. The spin coating of substrates before derivatization and synthesis with a ~0.4-μm film of 70–100-nm colloidal silica particles increases their surface area sevenfold. A presumed increase in probe density accounts for a corresponding increase in hybridization signal.^[54]

The effect of sequence defects on the hybridization performance of microarrays synthesized in situ has been studied with synthetic mixtures. It is not surprising that higher probe purity is projected to improve the performance of the microarrays.^[55] A variety of photochemically removable protecting groups have been investigated to address the shortcomings of the MeNPoc group in DNA synthesis, and their performance has been studied in simple photochemical solid-phase synthesis as well as on arrays (Scheme 8). These include the DMBoc,^[56] PyMoc,^[57] and NNEoc groups,^[57] all of which give 96 % cycle yields. It was recently reported that the NPPoc group gives quantitative cycle yields in photochemical synthesis on arrays, thus representing a significant advance.^[58] The mechanism of deprotection differs among these groups. The MeNPoc and NNEoc groups exhibit conventional nitrobenzyl photochemistry, and undergo oxygen migration from the nitro group to the benzylic position to form a nitroso hemiketal. Its further conversion into the nitrosocarbonyl produces a hemicarboxylate ester that decarboxylates to the alcohol. The DMBoc and PyMoc groups are thought to photosolvolyze to their cations and the hemicarboxylate. NPPoc is a relatively new group that is cleaved by a light-promoted beta-elimination process in the presence of mild bases. It is converted into the nitrostyrene and the hemicarboxylate.

The manufacture of Affymetrix Genechip microarrays is performed on 5-inch fused silica substrates that bear 50–400 replicate arrays, each of up to 1.6 cm² and with up to 400 000 probes. The deprotection of MeNPoc groups in each cycle requires less than 1 min and a filtered I-line (365 ± 10 nm,

1 kW) exposure system is used. The solvent-free cleavage of MeNPoc proves advantageous, as a contact printing process can be used in which the masks are placed directly against the wafer. Completed wafers are diced into individual arrays and packaged into a plastic carrier with ports that permit the addition of hybridization solutions. The feature size on current commercial chips is 50 μm, but the next generation technology will decrease that to about 25 μm.

An alternative photolithographic method developed by workers at Affymetrix in collaboration with IBM uses traditional semiconductor photoresists as a two-layer physical barrier to conventional chemical reagents for DNA synthesis (Figure 4).^[59] A standard DMTr-protected, derivatized glass

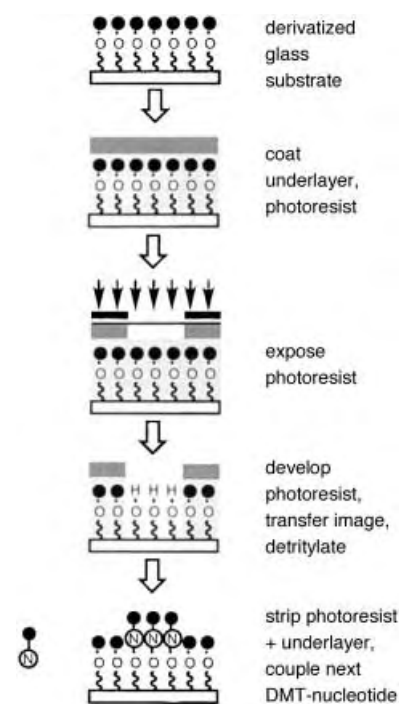
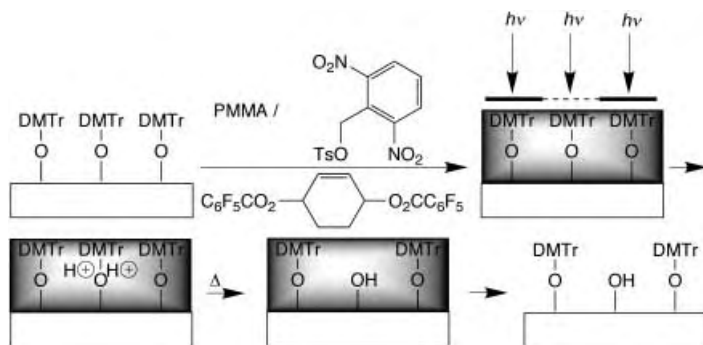


Figure 4. Photolithographic DNA synthesis with a bilayer resist system (reproduced from ref.^[59] with permission, Copyright (1996) National Academy of Sciences, USA).

surface was coated with a soluble polyimide (~0.5 μm) to protect the molecules from resist chemistry. The overlying negative-tone resist layer (~0.5 μm) is an epoxy resin combined with a photochemical acid generator that cross-links the resin, thus making it insoluble. This strategy draws on substantial experience in acid-generating chemically amplified resist systems that are currently used in submicron lithography for computer chips.^[60] Here, photogenerated acid (PGA) enabled the ready production of 4-μm features. The epoxy was developed from unexposed areas with cyclohexanone, and the underlying polyimide was stripped off with anisole. Detritylation of 5'-DMTr protecting groups used dichloroacetic acid in cyclohexanone to avoid dissolving the polyimide. Dissolution of all polymers in chlorinated solvent prepared the surface for phosphoramidite coupling, which proceeded in 90 ± 5 % yield per step. Microarrays of decanucleotides in 100-μm features that were prepared by using this

protocol showed comparable performance with those prepared with MeNPoc.

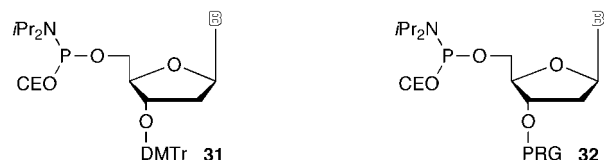
A different approach to light-directed DNA synthesis uses conventional acid-sensitive hydroxy-protecting groups with chemically amplified, PGA polymer films (Scheme 9).^[61] Initial *p*-toluenesulfonic acid production then generates two equivalents of pentafluorobenzoic acid, which is sufficiently



Scheme 9. DNA synthesis by photogenerated acid. Ts = toluene-4-sulfonyl, PMMA = polymethylmethacrylate.

acidic to deprotect DMTr groups without affecting the purine nucleosides. Since the deprotection of DMTr groups is catalytic in acid, which is diffusible, it might be feared that PGA could cause indiscriminate deprotection. However, a polymethyl methacrylate film limits lateral diffusion and permits the production of spots that are smaller than 10 μm . The cycle yields thus far reported with this method are about 90%, still much lower than desirable. An attractive aspect of this method is that the chemical amplification in the acid generation step results in a nonlinear dependence of deprotection on photon dose. This nonlinearity of photochemical response is key to the production of small features in conventional lithographic methods.^[62]

The reverse direction of synthesis (see Section 2.1) to give DNA with free 3' ends can be addressed by exchanging the protecting group and the phosphoramidite group in the monomer units, and usually by lengthening coupling cycles (Scheme 10). Workers at Affymetrix recently reported methods for the preparation of monomer units that bear 5'-phosphoramidites and 3'-MeNPoc groups (**32**, Scheme 10) for



Scheme 10. Amidite reagents for reverse synthesis of DNA with free 3' ends. PRG = MeNPoc, NPPoc.

this purpose.^[50] This strategy has also been applied to the NPPoc group to give, with high fidelity, sequences that can be used in enzymatic processing.^[63] In principle, the newer methods of acid-based photochemical deprotection should

also make DNA arrays with free 3'-ends more accessible, as the 3'-DMTr-5'-phosphoramidites (**31**, Scheme 10) are commercially available. This also makes clear the advantage of using conventional monomer units, which can be purchased for many nucleotide analogues with a wide variety of base and sugar modifications.

Two groups have sought to replace the static masks used in the Affymetrix method with dynamic programmable devices that are somewhat similar to computer overhead projection systems. A digital micromirror array was used at the University of Wisconsin^[64] in a projection optics system that has been commercialized by NimbleGen (Figure 5). A similar

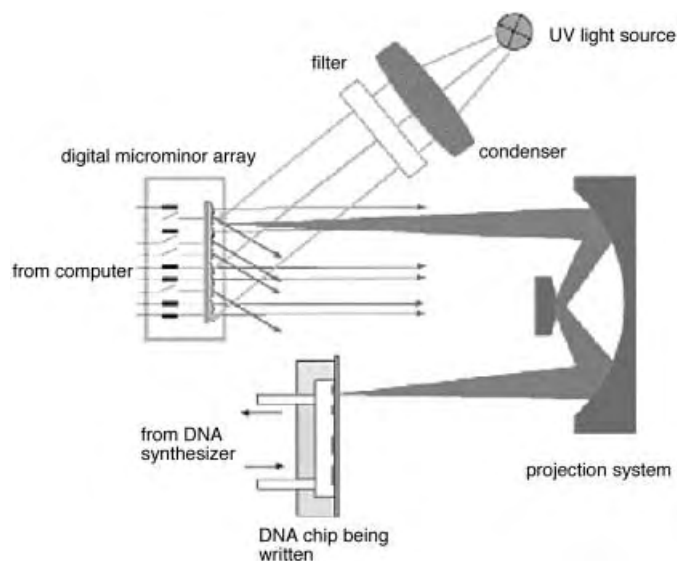


Figure 5. Reflective optics for photolithography with micromirror arrays (reproduced with permission from ref.^[64]).

technique was used at the University of Houston^[65] and is being commercialized by Xeotron. The primary patterning device employed in this method is actually a $1.5 \times 1.5 \text{ cm}^2$ glass surface with fluorocarbon streets surrounding up to 48×48 synthesis regions with microwells as small as 300 μm . These substrates are made by using the Protogene methods described in Section 3.2, followed by derivatization with HBPTES (**8**, Scheme 1). The synthesis begins the coupling of two T bases by using conventional acid deprotection chemistry. Immersion of the chip in a solution of photogenerated acid precursor leaves liquid droplets behind in the microwells after draining. Photochemical DMTr deprotection, which was demonstrated in solid-phase DNA synthesis (>92% cycle yields),^[66] is directed in particular microwells with a 480×640 array of $16 \times 16 \mu\text{m}^2$ micromirrors to project the light. Optimization of deprotection efficiency based on the number of 5'-hydroxy groups created (measured by fluorescein derivatization by using the Affymetrix method) showed that the superior photoacid cocktail was composed of a diaryl iodonium salt (with a short wavelength λ_{max}) and a thioxanthone sensitizer (that absorbs the radiation) in dichloromethane. With this method, oligonucleotides with up to 30 residues have been prepared.

3.2. Jets

As an alternative to directing the chemistry to microscopic sites with light, reagents for conventional DNA synthesis can be directed by using the same methods described in Section 2.1.2 for the delivery of complete oligonucleotides. Early contributions to this area were made by researchers at Combion by using coaxial piezoelectric/glass capillary jets (Figure 6).^[67] A polyethylene glycol linker that bears a DMTr group is attached to the surface. A jet dispenses the

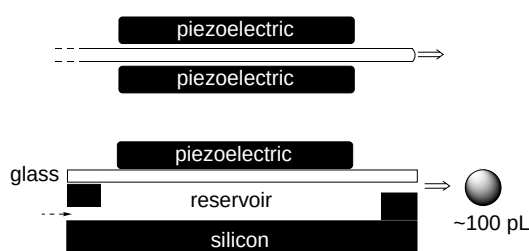
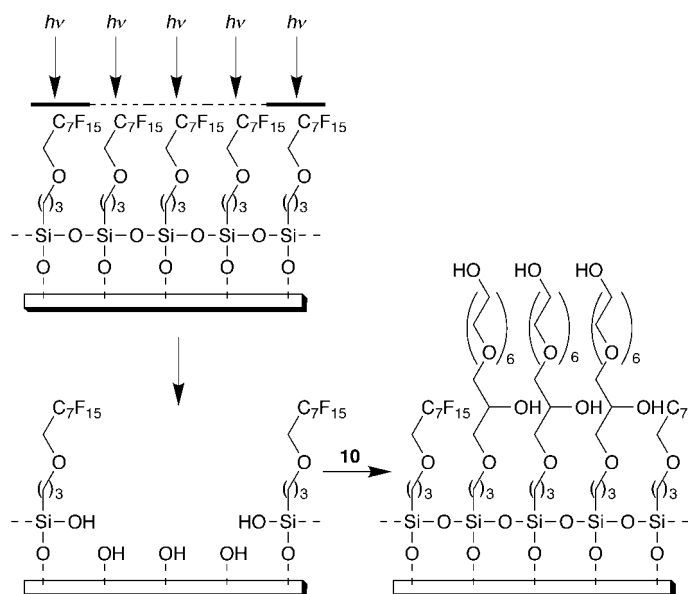


Figure 6. Piezoelectric glass jets for reagent delivery.

deprotecting reagent upward to sites intended for synthesis on the horizontally held substrate. It is moved to a vertical position for rinsing and mounted in a flow cell attached to a DNA synthesizer for coupling reactions. The overall cycle lasts 10 min. A conservative estimate of the yields in each of the steps in this process is 91 %. These workers also identified a difficulty in using volatile solvents such as acetonitrile with jets, and instead used ZnBr_2 in CH_2Br_2 /isopropanol as a less volatile yet equally effective alternative deprotectant.

The Protogene method isolates the synthesis areas from each other by using nonwetting regions or streets that bear fluoroalkanes (Scheme 11).^[68] Several steps are involved in the production of a glass microarray plate: gas-phase coating



Scheme 11. Preparation of a surface with synthesis regions surrounded by nonwetting “streets”.

with POPTS (9, Scheme 1), exposure through a mask to a CO_2 laser to ablate the silane, preparation of the patterned regions for synthesis by derivatizing with GPTS, and opening of the epoxide with hexaethylene glycol (HEG). Piezoelectric impulse jet pumps produced as a microelectromechanical system (MEMS) are the second novel aspect of this method. A reservoir, inlet, and nozzle are produced as three-dimensional features in a ceramic (Figure 6). To form a chamber, the ceramic is bonded to a flexible top plate, to which a piezoelectric element is attached. When the piezoelectric is energized, it deforms the reservoir like a bellows, which ejects fluid at a velocity of $1\text{--}10\text{ ms}^{-1}$. A nozzle size of $40\text{ }\mu\text{m}$ produces acetonitrile droplets of about 33 pL ($\pm 5\%$), of which three will fill a $50\text{-}\mu\text{m}$ diameter synthesis site. These pumps operate at up to 3 kHz , can hit a $250\text{-}\mu\text{m}$ target at a distance of 2 cm , and can be ganged together in printheads (up to 64 nozzles with a $400\text{-}\mu\text{m}$ pitch) to create independently controllable jets that deliver the same reagent from a common reservoir. The printheads are stacked to provide each base as its phosphoramidite or H-phosphonate monomer, along with the appropriate activator for oligonucleotide synthesis. The pumps remain stationary during synthesis and the microarray is moved below them with an X,Y table. With a repetition rate of 1 kHz , the pumphead can deliver monomer units to a 512×512 array (262000 sites) in only 32 seconds! The synthesis sites have a surface tension of 47 dyne cm^{-1} , and more closely match that of acetonitrile (29) than that of the streets (18), thus preventing mixing between adjacent sites. The common synthesis, washing, capping, DMTr deprotection, and final phosphite oxidation/deprotection steps, can be performed as batch operations across the whole microarray simultaneously. Cycle times are 6 min per residue.

Workers at Rosetta use a similar technology to micro-fabricate monolithic jets that will deliver 100-pL volumes from glass, silicon (10–100- μm nozzle), and piezoelectric ceramic.^[69] Another aspect of their method is the use of propylene carbonate as solvent for the synthesis because of its high surface tension ($> 30 \text{ dyne cm}^{-1}$), low volatility, and high viscosity.^[70] Microarrays of more than 25 000 different 60-mers can be made with this technique and are now available commercially from Agilent.

3.3. Physical Masking

These techniques are similar to stencils and were extensively described in an earlier review.^[2] They are produced primarily at the University of Oxford and at Beckman; these groups have also cooperated. Researchers at Beckman developed a unique surface attachment **11** (Scheme 1)^[71] by the treatment of a polypropylene sheet with ammonia in a plasma. This introduces tertiary amine functions that can be directly treated with nucleoside phosphoramidite monomers to produce phosphoramidates after oxidation. A sequence of ten T residues is used as a linker. The sheets can be cut into 2-mm strips to create “dipstick” arrays. Protocols have been provided by the group at Oxford University for the preparation of arrays on aminated polypropylene (AP) or glass,^[72] including the GPTS/HEG-derivatized glass **10** (Scheme 1)

that does not permit the oligonucleotide to be detached. Polypropylene must be mounted on a glass slide to make it rigid enough to seal against the stencil and for reliable translation relative to it. Polypropylene arrays have been prepared by using 3'-DMTr-5'-phosphoramidites **31** (Scheme 10) that create free 3' ends for enzymatic processing.^[73] A drawback of this method is that the hybridization data are not as unambiguously and as easily interpreted as conventional microarray data.

4. Summary and Outlook

With many methods available to produce microarrays, the strengths and weaknesses of each should be considered. Arrays spotted from cDNA and those derived from synthetic oligonucleotides (either synthesized and spotted or synthesized in situ) have significantly different uses. One requires a cDNA in one's own lab to generate the former. This method is common in biology laboratories that are interested in generating custom microarrays, and also offers longer probes, which some workers prefer. The use of synthetic oligonucleotides means that probes can be designed based only on a sequence found in the genetic databases. However, the efficiency of the synthesis limits their length, currently around 60 nucleotides by any method. A significant question is whether there is a preferred method for microarray production and analysis, and this cannot be answered without knowing the individual needs and resources. The performance of 50-mer oligonucleotide arrays versus arrays of cDNAs/PCR products with more than 300 base pairs has shown no difference.^[13]

An area for continued investigation is quality control and monitoring methods for chemical reactions at/on microarray surfaces. Many different techniques have been applied to the chemically based research on DNA microarrays, but most often these are not fast enough to be used as part of routine laboratory operations by nonspecialists, or they require quite sophisticated instrumentation that is not available to most chemists and biologists. Because of the success of SPR techniques in studying other types of biological recognition events (e.g., in BiaCore instruments), SPR imaging offers great promise for future microarray use. The novel technique of reflectometric interference spectroscopy may be likewise applicable.^[74]

Surprisingly, another area in which continued improvements are needed for DNA arrays is in oligonucleotide synthesis, usually considered to be a "perfected" technology. Whether the issue is cycle efficiency in photolithographic synthesis or the purity of an oligonucleotide prepared by conventional automated synthesis with some novel functionality for attachment, many workers find that synthesis failures still cause problems in microarray production.

There is certainly a drive to produce smaller probe sites for reasons described in Section 2. Even femtoliter volumes can now be delivered to make spotted arrays with 20- μ m features.^[75] However, there is a limit to which making smaller sites will assist microarray analysis, because the detection methods for the products are optical and diffraction-limited.

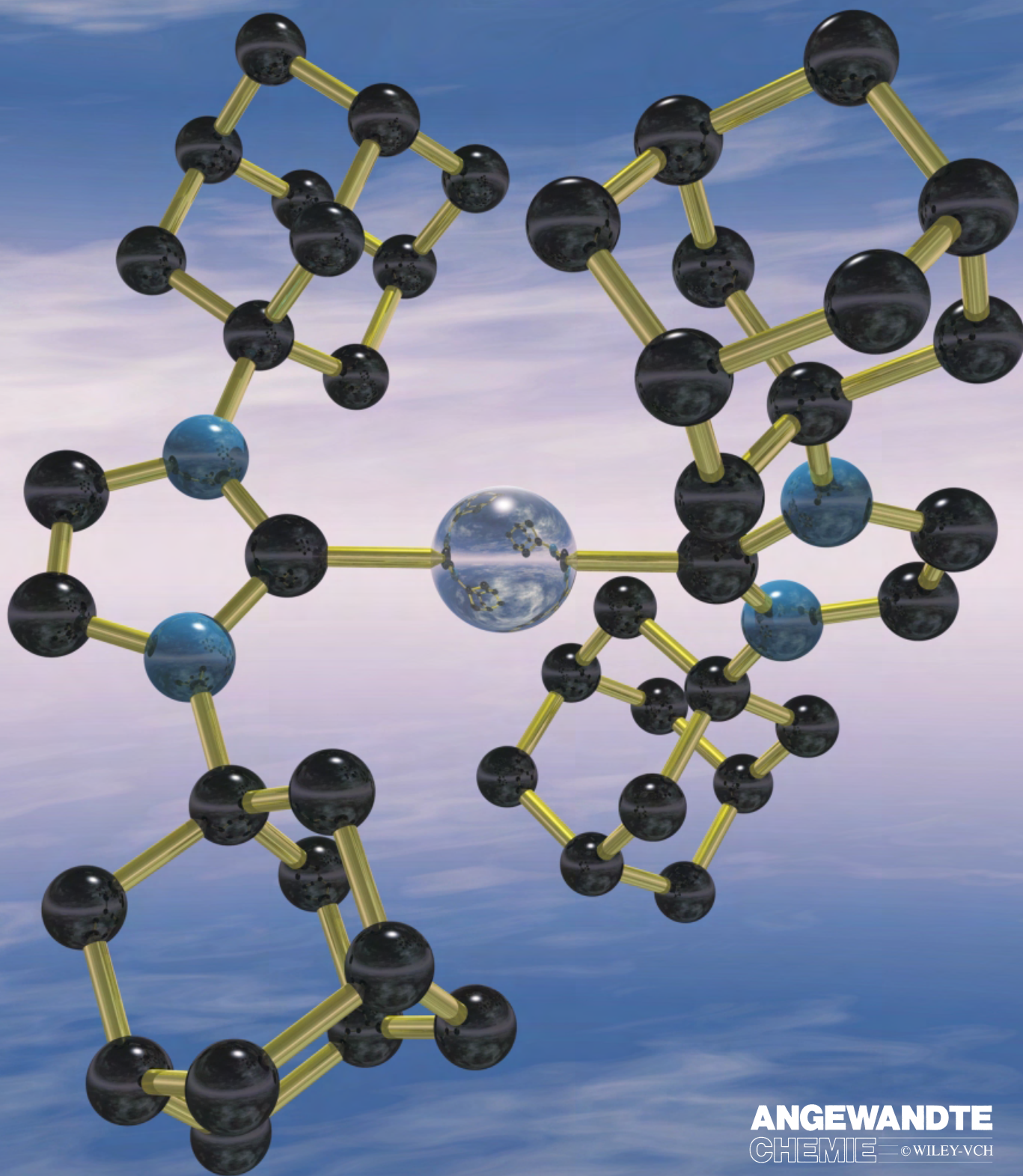
Even if 1000-nm probe sites could be made, a statistically valid number of data points from interrogation of such a site with 650-nm radiation would be very difficult to obtain. Density improvements in production will require commensurate improvements in the spatial resolution of detection.

Received: August 18, 2001 [A488]

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N-Heterocyclic carbenes as ligands for
metal complexes – challenging phosphane
ligands in homogeneous catalysis



N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis**

Wolfgang A. Herrmann*

In memory of John Osborn

N-Heterocyclic carbenes have become universal ligands in organometallic and inorganic coordination chemistry. They not only bind to any transition metal, be it in low or high oxidation states, but also to main group elements such as beryllium, sulfur, and iodine. Because of their specific coordination chemistry, N-heterocyclic carbenes both stabilize and activate metal centers in quite different key catalytic

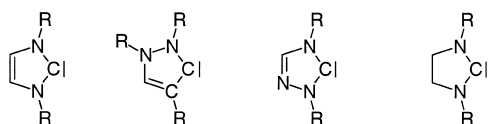
steps of organic syntheses, for example, C–H activation, C–C, C–H, C–O, and C–N bond formation. There is now ample evidence that in the new generation of organometallic catalysts the established ligand class of organophosphanes will be supplemented and, in part, replaced by N-heterocyclic carbenes. Over the past few years, this chemistry has been the field of vivid scientific competition, and yielded pre-

viously unexpected successes in key areas of homogeneous catalysis. From the work in numerous academic laboratories and in industry, a revolutionary turning point in organometallic catalysis is emerging.

Keywords: carbene ligands • carbenes • heterocycles • homogeneous catalysis

1. Introduction

Since the first report by Öfele in 1968,^[1a] the metal coordination chemistry of N-heterocyclic carbenes **A–C**, derived from imidazole, pyrazole, and triazole has had a long, steady history in our laboratory. Numerous metal compounds



A **B** **C** **D**

were synthesized and characterized before the free carbene ligands became available through the important work of Arduengo et al.^[2] A series of Ph.D. theses^[3, 4] yielded a large number of publications. The related C–C-saturated carbenes **D** (e.g., R = neopentyl) resulting from “Wanzlick dimers”^[5] were investigated in terms of their organometallic chemistry by Lappert and his associates.^[6]

The ylidenes **A–D** are nucleophilic singlet carbenes. They have been attached to metals either from the corresponding azolium salts (**A–D**) or from “Wanzlick dimers” (**D**), ever since the pioneering work of Öfele^[1a] and Wanzlick^[1b] appeared in the literature. Since N-heterocyclic carbenes are now available as “bottle-able compounds” (a phenyl-substituted triazole-derived ylide of type **C**^[21] is the first carbene to be commercially available^[**]), their inorganic and organometallic chemistry has gained enormously in versatility and depth.^[7]

2. Early Breakthroughs

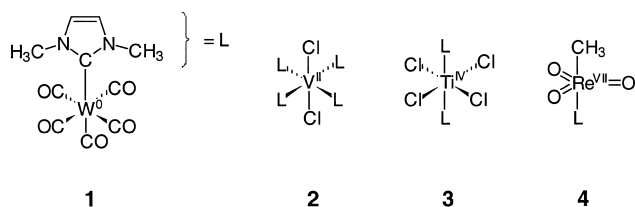
In 1992/93, we noted the striking similarity of electron-rich organophosphanes PR_3 and N-heterocyclic carbenes (NHCs) in terms of their metal coordination chemistry, particularly the ligand properties and metal complex synthesis.^[8–10] It was pointed out that both low- and high-oxidation-state transition metals are compatible with the “Wanzlick–Öfele carbenes,”^[***] with typical examples being represented by the well characterized species **1–4**.

[*] Prof. Dr. W. A. Herrmann
Anorganisch-chemisches Institut
Technische Universität München
Lichtenbergstrasse 4
85747 Garching, Munich (Germany)

[**] N-Heterocyclic Carbenes, Part 31; part 30 ref. [80].

[**] Acros Organics, Dat. No. 30226-0010.

[***] Hans Werner Wanzlick (Berlin) and Karl Öfele (Munich) published the first transition metal complexes (Hg and Cr, respectively) back in 1968.^[1a,b] In spite of Arduengo’s breakthrough isolation of the free carbene (1991), we assign the term “Wanzlick–Öfele carbenes” to recognize their pioneering work in this area.



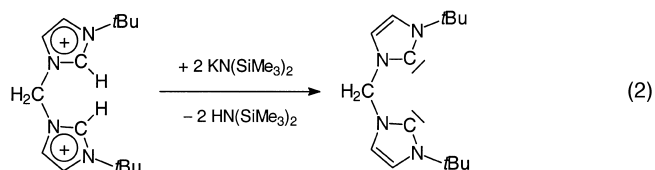
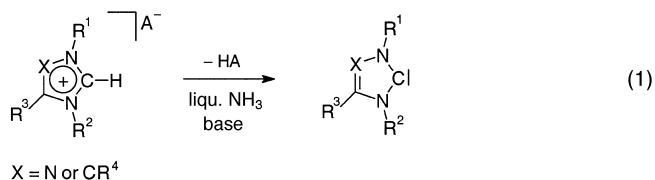
Spectroscopic studies revealed the close relationship of NHCs and organophosphanes.^[9–12] They are both pronounced σ -donor ligands with only little backbonding character. Regarding the theory of their bonding, the NHCs are best treated as “diaza–allyl systems”, with little π aromaticity being present in the C–C and CN unsaturated species **A–C**.

Four initial key patents were filed with priority of December 29, 1994.^[13–16] They cover transition metal complexes of Group 8–10 elements exhibiting N-heterocyclic carbenes including imidazole- and pyrazole-derived carbenes as well as chelating dicarbene ligands.^[13] A catalytic procedure to generate aldehydes by hydroformylation with catalysts containing N-heterocyclic carbenes was disclosed in the second patent.^[14] The catalytic C–C coupling to make aromatic aldehydes with the same catalysts (e.g., hydroformylation and related coupling reactions) is covered by the third patent,^[15] and the fourth reports novel complexes of the lanthanoid metals including scandium and yttrium.^[16]

Somewhat later, the generation and large-scale synthesis of pure N-heterocyclic carbenes was described (“ammonia method”):

- Liquid ammonia or mixtures of liquid ammonia with organic amines or polar-aprotic solvents were used as solvents,
- to smoothly and quantitatively deprotonate the corresponding azolium salts
 - with reagents such as metal hydrides, -amides, -alkoxides, and -carboxylates
 - at temperatures between -75 and 0°C .^[17]

This technique following Equation (1) also applies to large-scale syntheses. It includes deprotonation agents such as the commercial $\text{K}^+[(\text{CH}_3)_3\text{SiNSi}(\text{CH}_3)_3]^-$ and $\text{Li}^+[\text{N}(\text{iC}_3\text{H}_7)_2]^-$ that, for example, selectively generate chelating dicarbenes but leave methylene and other hydrocarbon bridges intact^[18] [Eq. (2)]. The high-yielding synthesis of novel, functionalized



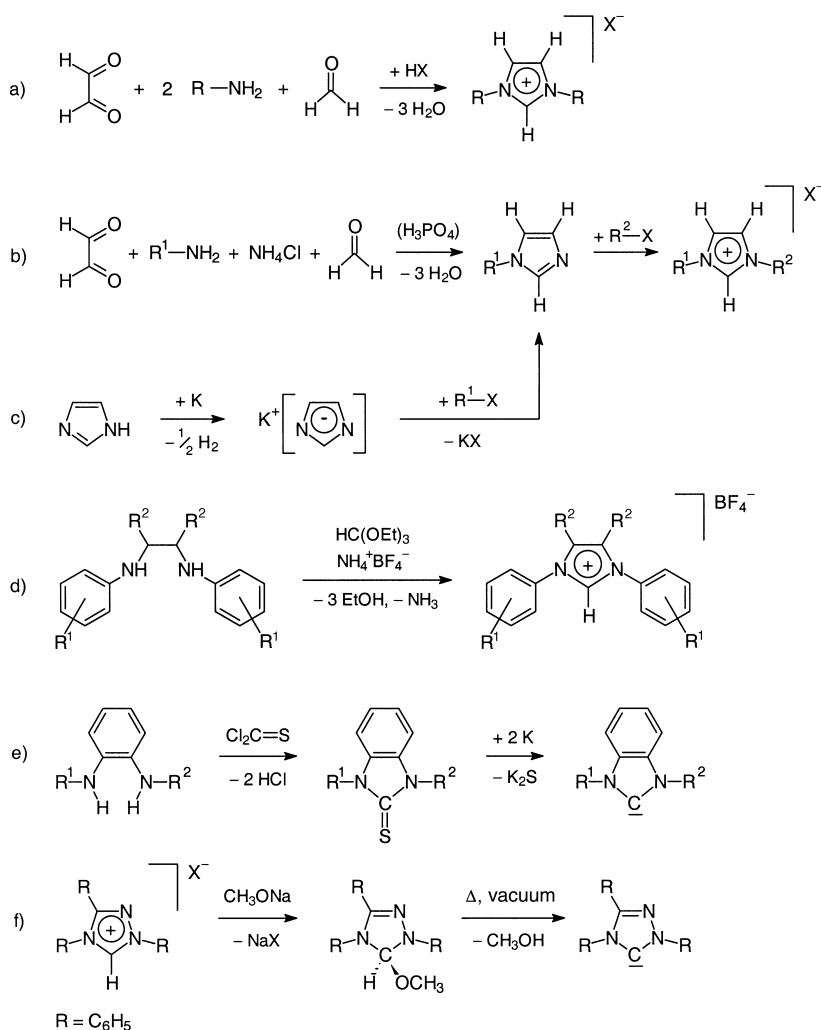
N-heterocyclic carbenes in liquid ammonia was described in detail as the standard literature technique in 1996.^[19] Other techniques include the use of potassium hydride or potassium *tert*-butylate in THF to deprotonate the azolium precursor cations.^[2c] Care has to be taken with the choice of the deprotonating agent, because certain hydrides yield imidazolidines ($+ \text{H}^-$) instead of the carbene.^[2c]

3. Easy Access

Most easily available are stable carbenes derived from imidazole, not least because numerous imidazolium precursor compounds can be made along various reliable routes. The one-pot synthesis starting from glyoxal, primary amine, and formaldehyde is straightforward (Scheme 1 a), its variation (Scheme 1 b) allows unsymmetrically N-substituted derivatives (R^1 , R^2) to be made, while in another route (Scheme 1 c) the imidazolidine anion is alkylated by reactive alkyl-/aryl halides (or -triflate derivatives). The orthoformate route (Scheme 1 d) converts the easily accessible 1,2-diamines (e.g. from Pd-catalyzed Buchwald coupling) into the aryl-substituted imidazolium salts. The heterocycle synthesis according to Scheme 1 a and b was previously mentioned in the literature.^[20] The desulfurization of the cyclic thiourea derivatives (Scheme 1 e) depends on relatively drastic conditions but works well in many cases, for example, benzimidazolin-2-ylidenes from the corresponding 2-thiones.^[5b] Vacuum ther-



Wolfgang A. Herrmann was born 1948 in Kelheim/Donau (Germany) and received his organometallic academic education with E. O. Fischer (Munich), H. Brunner (Regensburg), and P. S. Skell (Pennsylvania State University) before he became a professor of chemistry at the university of Regensburg (1979) and then Frankfurt (1982). In 1985 he was appointed the professor of inorganic chemistry at Technische Universität München to succeed E. O. Fischer. His research is focused on homogeneous catalysis, with a strong synthetic, spectroscopic, and structural background. He has authored approximately 550 scientific publications, numerous patents, and a number of review articles. He holds honorary doctorates from the Lyon, Veszprém, and South Carolina universities (1990/1995/1999) as well as numerous scientific awards, for example the Leibniz Award of the DFG, the Wilhelm Klemm Award of the German Chemical Society, the Alexander von Humboldt Award, the Max Planck Research Award, the Bundesverdienstkreuz, and the Ordre d'Honneur of the President of France. Professor Herrmann is a member of the editorial board of *Angewandte Chemie*.



Scheme 1. Convenient synthetic routes to imidazolium salts and imidazol(2)-ylidenes derived therefrom.

molysis of methoxy derivatives (Scheme 1 f) yields carbenes in good yields, as well, for example, 4,5-dihydro-1*H*-1,2,4-triazol-5-ylidenes.^[21]

The free carbenes **A** and **D** are stable to air. Their “air sensitivity” is in fact hydrolysis. It is reported that **D** hydrolyzes instantaneously, while **A** is much more robust because of “aromatic stabilization”.^[22] Hydrolysis yields acyclic products by C–N bond cleavage.^[22]

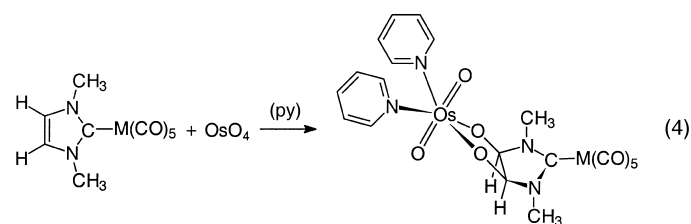
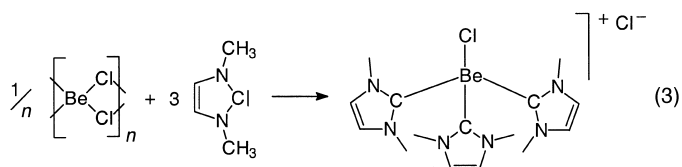
4. Metal Coordination Chemistry

N-heterocyclic carbenes in fact behave like typical σ -donor ligands that can substitute classical $2e^-$ donor ligands such as amines, ethers, and phosphanes in metal coordination chemistry.^[23–32] It was determined in 1993 that “heterocarbenes show bonding properties similar to those of trialkylphosphanes and alkylphosphinates”.^[9] Nolan et al. concluded from structural and thermochemical studies that “in general these ligands behave as better donors than the best phosphane donor ligands with the exception of the sterically demanding (adamantyl) carbene”.^[118]

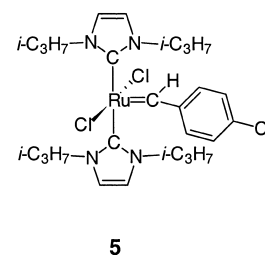
Examples are the “titration” of $\text{TiCl}_4 \cdot 2\text{PR}_3$ with two NHC equivalents to give $\text{TiCl}_4 \cdot 2\text{NHC}$, or of $\text{VCl}_2 \cdot 4\text{NR}_3$ with four equivalents to yield $\text{VCl}_2 \cdot 4\text{NHC}$.^[26a] The typical examples **1–4** result from the free carbenes. The complexation to beryllium chloride^[11] is typical in that the analogy to other σ -donor ligands is evident [Eq. (3)]. Other alkaline-earth metal complexes of NHCs were described by Schumann et al.^[33]

Metal complexes of alkylidene-bridged dicarbenes followed soon.^[12] Also, the first chemistry occurring at the five-membered heterocycles was reported, for example, the OsO_4 -addition to the C–C unsaturation [Eq. (4)].^[4b, 23] This latter reaction once again indicates that there is little to no π -aromaticity in the five-membered ring, quite consistent with recent charge-density studies.^[34]

Numerous molecular structures were determined by single-crystal X-ray diffraction. It was shown that there is little or no variation in the geometrical details of the NHC ligands from case to case. The metal–carbene bonds are rather long (>210 pm), while in Fischer- and Schrock-type complexes these distances are significantly below 200 pm because of pronounced backbonding (“double bond”). An excellent benchmark structure is the olefin metathesis catalyst **5** which exhibits both types of carbenes (Figure 1). As a result of this particular bonding situation, nucleophilic NHCs can, depending on the steric situation, rotate around the metal–carbon axis.



M = Cr, Mo, W; py = pyridine



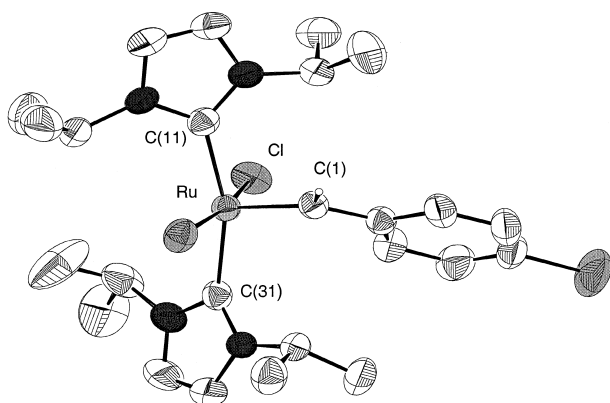
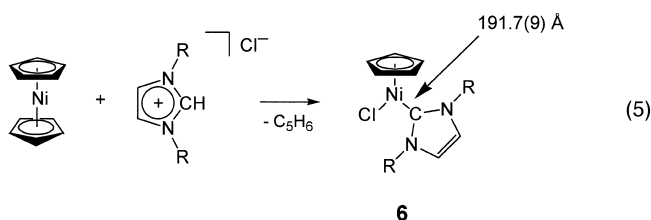


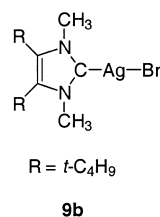
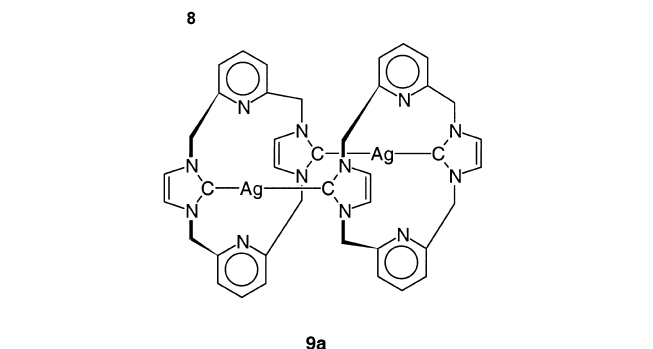
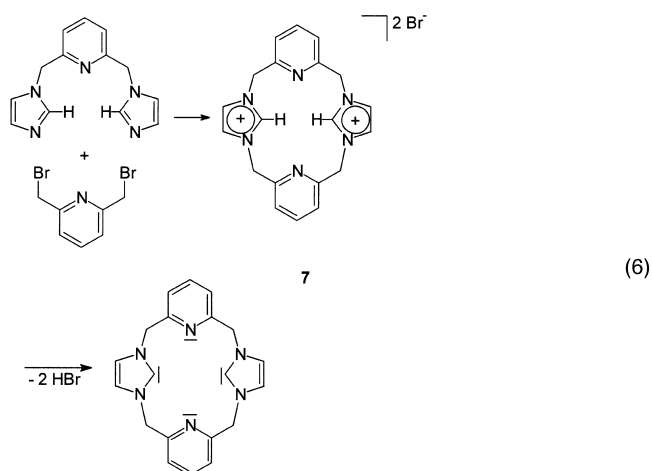
Figure 1. ORTEP representation of the molecular structure of the olefin metathesis catalyst **5**. Selected bond lengths [pm]: Ru–C(11) 210.7(3), Ru–C(31) 211.5(3), Ru–C(1) 182.1(3).^[4k]

Full reports on the synthesis of metal complexes that are relevant to catalysis appeared in 1996 and the following year.^[24–32] While in most cases imidazolyn-2-ylidene complexes were described, several triazol-derived systems were reported, too.^[21, 95] Salt metathesis and elimination reactions represent the prevailing synthetic access to NHC and related metal complexes. Regitz gave a first review in 1996.^[35] A recent exploitation of the azolium route now covers metallocenes, such as **6** [Eq. (5)], and works for both nickelocene and chromocene. Another field of application has thus been opened.^[36]

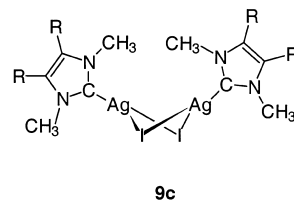


The first carbene-linked cyclophane **8** was made by Youngs et al.^[37] from the ionic bis(imidazolium) precursor compound **7**, which results from a straightforward alkylation reaction of 2,6-bis(imidazolomethyl)pyridine [Eq. (6)]. Silver oxide was used to deprotonate **7** and, at the same time, introduce the metal center which adopts a linear coordination environment in the binuclear complex **9a** (X-ray diffraction study).^[37] Monomeric and dimeric silver halide complexes **9b** and **9c**, respectively, are obtained in the same way,^[38] while the existence of NHC–copper(I) complexes, such as **9d**, seems to depend on chelating properties of the ligands.^[39] A tetranuclear, ionic complex of formula $[\text{Ag}_4\text{L}_2][\text{PF}_6]_4$ is derived from the N,N,C,C-macrocycle **8**.^[40]

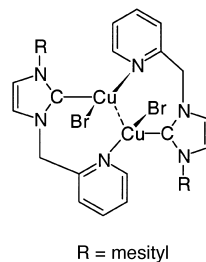
Special NHC-transfer reagents are the silver(I) complexes of type **9e**. They are formed in a simple way by treatment of Ag_2O with imidazolium salts^[41] and transfer their NHC ligands to other metals, for example, palladium.^[42] This technique seems to be particularly effective in the case of functionalized NHCs with “dangling” substituents. Related nickel and palladium cyclophane-type complexes of the NHC series have recently been made.^[43]



9b

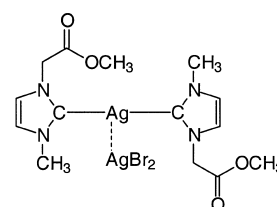


9c



R = mesityl

9d



9e

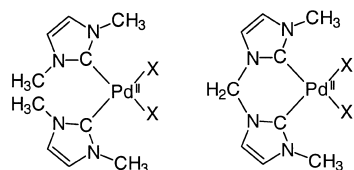
5. Catalytic Properties

After the initial patent reports, catalytic data were released in a series of publications, the first of which appeared in 1995.^[44]

5.1. Heck and Suzuki Coupling

First, the Heck coupling of aryl bromides and aryl chlorides was communicated: Complexes **10** and **11** are active upon

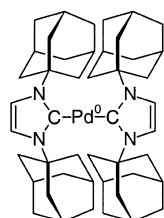
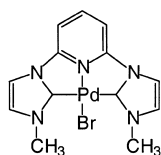
smooth reduction with formate or hydrazine, thus generating the active Pd^0 species. Unexpected were the low catalyst loadings (ca. 10^{-3} mol %) necessary to obtain yields $> 99\%$ in the case of bromides, and 0.1–1 mol % for aryl chlorides.^[44] The advantageous properties of the “New structural principle

**10a-c****11a-c**

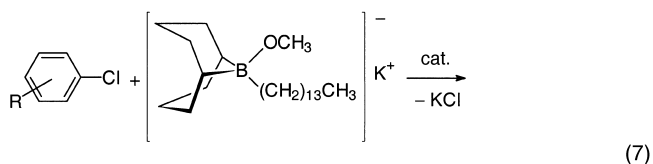
a: X = Cl; **b:** X = Br; **c:** X = I

for catalysts in homogeneous catalysis”^[44] was stated as follows: “The new catalyst type described here has a series of advantageous properties and potential for development: a) high thermal and hydrolytic durability resulting from exceptionally stable M–C bonds (long shelf-life, stability to oxidation); b) easy accessibility, and c) no need for an excess of the ligand. The prospects for derivatization to water-soluble catalysts (two-phase catalysis), immobilization, and chiral modification seem promising because of the constitution of the ligands.”^[44] These predictions have since been shown to be correct.

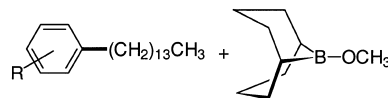
The phosphane-free NHC catalyst **12a**, either as the isolated complex or generated in situ, represents the most active coupling agent for aryl chlorides to form (substituted) biphenyls in the Suzuki cross-coupling. Reaction times between two and 48 h are sufficient at room temperature, while at 80°C the productivity is approximately six times better.^[45] The stability of the active catalyst **12b** is a result of the “pincer-type” tridentate C,N,C-ligand.^[122]

**12a****12b**

A general and user-friendly procedure for Suzuki reactions with aryl chlorides is now based on easy-to-make NHC–palladium catalysts. As shown by Fürstner et al.,^[46] subtle steric effects in the NHC ligands govern the *B*-alkyl Suzuki–Miyaura coupling,^[129] with the best results being obtained from the 1,3-di-2-propyl derivative [Eq. (7)], as “imidazolium additive”. In several cases, the in situ technique is more efficient than the use of the preformed palladium catalyst. Other borate complexes with $c\text{-C}_3\text{H}_5$, $\text{C}\equiv\text{C-C}_6\text{H}_5$, and $\text{CH}_2\text{CH=CH}_2$ in place of $(\text{CH}_2)_{13}\text{CH}_3$, perform similarly well.



(7)



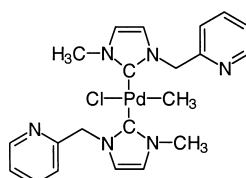
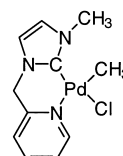
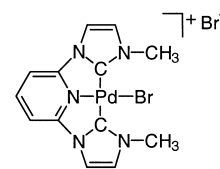
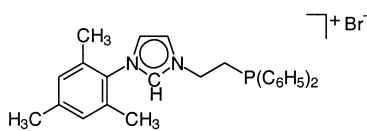
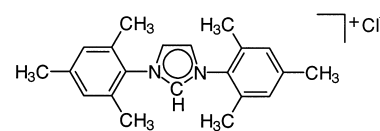
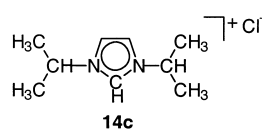
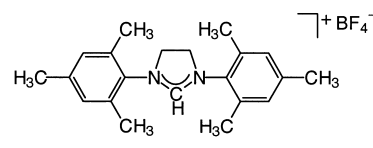
R = H, 3,5-(OCH_3)₂, 4- CO_2CH_3

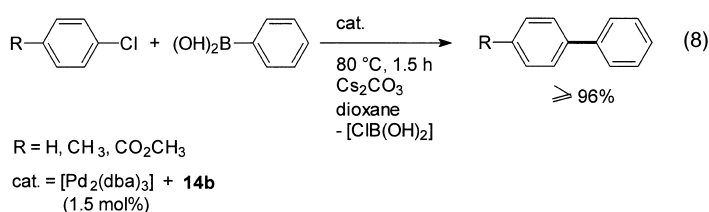
cat. = $\text{Pd}(\text{OAc})_2$ + **14c**
(2 mol%) (4 mol%)

Highly active and very stable catalysts for Heck, Suzuki, and Sonogashira coupling reactions were discovered in certain palladium(II) complexes of NHCs with “dangling” *N*-substituents: Catalyst **13a** performed particularly well, giving turnover numbers (TONs) of 1.7×10^6 (Heck) and 1.1×10^5 (Suzuki) at $> 85\%$ conversion of 4-bromoacetophenone with butyl acrylate and phenylboronic acid, respectively.^[42]

After first reports on the Suzuki cross-coupling activity of carbene ancillary ligands involving aryl bromides and activated aryl chlorides,^[47] non-activated, functionalized aryl chlorides were coupled successfully.^[48] Typical examples are shown in Equation (8); dba = *trans,trans*-dibenzylidenacetone. The sterically demanding 1,3-bis(mesityl)imidazol-2-ylidene (generated in situ from the imidazolium chloride **14b**) proved to be the best choice of ligand at palladium(II) centers. The C–C saturated azolium salt **14d** is now commercially available.^[*]

[*] Strem Chemicals, Inc. (Kehl, Germany).

**13a****13b****13c****14a****14b****14c****14d**



High efficiencies in Heck reactions of aryl bromides were reported by the Nolan group^[49] who used palladium in the presence of C,P-chelating NHC ligands derived from the sterically demanding imidazolium salt **14a**. A catalyst loading of 0.5 mol % based on palladium was sufficient to obtain good yields. Cesium carbonate turned out to be the most efficient base, much better than KOtC_4H_9 , NaOAc , and K_2CO_3 .^[49]

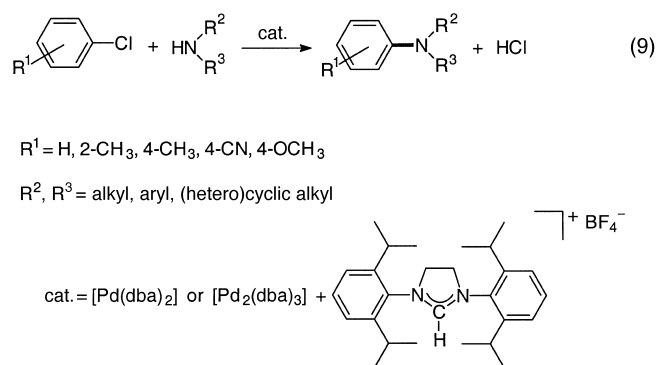
Exceptionally stable nickel and palladium complexes derive from imidazolium-linked *ortho*-cyclophanes.^[43] They catalyze Heck and Suzuki coupling reactions of aryl bromides and iodides with remarkable activities (TONs 7.1×10^6 for iodobenzene/*n*-butylacrylate at 140°C ; 6.8×10^5 for 4-bromonitrobenzene/*n*-butylacrylate at 140°C).

Mixed NHC–phosphane complexes of palladium(II) provide an excellent means of increasing both the activity and stability of the active species in C–C coupling reactions of this type. An important feature seems to be the necessity of bulky NHC ligands, whereas the phosphane has to be optimized for each type of reaction.^[119]

Numerous papers confirm the extraordinarily high thermal robustness of NHC catalysts. For example, the bis(carbene)–palladium(II) catalyst **13c** (X-ray diffraction study) maintains activity in the Heck coupling at least of aryl bromides at 184°C (!) in air.^[124]

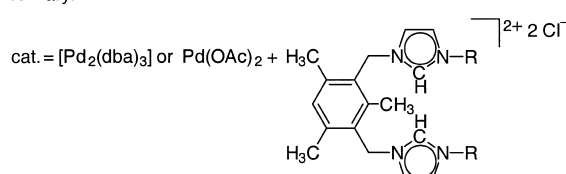
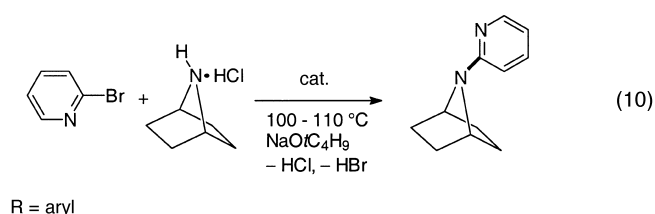
5.2. Aryl Amination

Through the use of NHC catalysts the palladium-catalyzed amination of aryl halides has experienced remarkable advances in substrate scope and reaction rates. Aryl chlorides are the most desired starting materials, simply for economic reasons. Nolan et al. have introduced a sterically hindered version of imidazolylidenes in the presence of palladium(0) complexes, albeit elevated temperatures are necessary to achieve good results.^[50] Instead, Hartwig's group used the dihydroimidazolylidene, see Equation (9), and obtained



yields near quantitative at room temperature when strong bases such as NaOtC_4H_9 were used to deprotonate the ligand precursor [Eq. (9)].^[51] TONs as high as 5×10^3 were obtained at elevated temperatures for the reaction of morpholine with an unactivated aryl chloride, for example, chlorotoluene (7 h, 100°C). Catalyst precursor ligands of type **14d** were used (2,6-diisopropyl instead of mesityl).

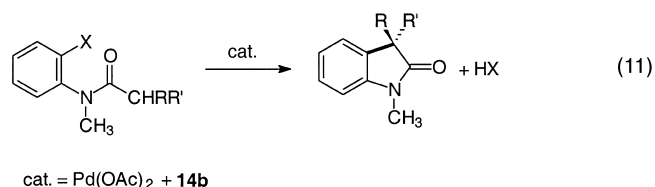
Readily available heteroaryl halides were used in the catalytic coupling with 7-azabicyclo[2.2.1]heptane. This useful type of cross-coupling amination once again employs NHC-based catalysts.^[52] A typical example is given in Equation (10).



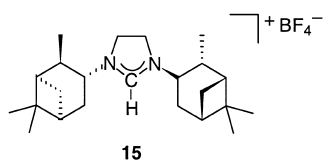
This reaction also works with heteroaryl chloride, albeit less efficiently. Any other ligand system tested so far (e.g., $\text{P}(\text{C}_6\text{H}_5)_3$, diphosphane ligands) is inferior under comparable conditions. Yields around 70% were achieved.^[52] The synthetic utility of the catalyst system seems to be broad and useful for the synthesis of *N*-arylamines. Also $[\text{Ni}(\text{acac})_2]$ in combination with sterically hindered NHC ligands catalyzes the amination of aryl chlorides.^[53] Future work must be aimed at avoiding the use of sodium hydride to regenerate the catalytically active nickel species.

5.3. Amide α -Arylation

Sterically hindered N-heterocyclic carbenes have become the ligands of choice for the palladium-catalyzed α -arylation of amides.^[54] The Hartwig group showed in an extensive study that cyclization reactions following Equation (11) give an

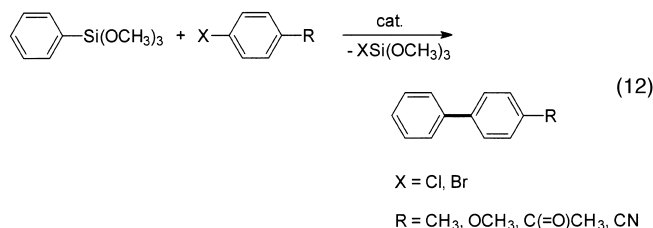


excellent performance—conversions and yields up to quantitative—when the bulky ligand precursor **14b** was employed in the presence of palladium(II) acetate. Enantiomeric excesses up to 67% were obtained when the chiral imidazolium salt **15** was used as a ligand precursor in the



cyclization of amides where $R^1 \neq R^2$. Chiral oxindoles, important substructures in numerous biologically active molecules, are thus catalytically accessible by easy means.^[54]

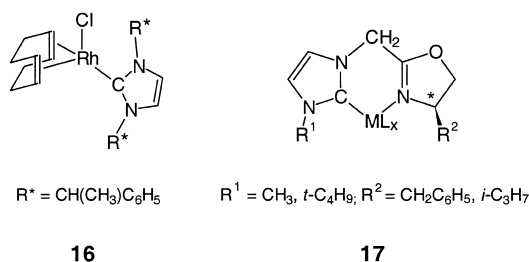
In an extension of common cross-coupling reactions, Nolan et al. have found that methoxysilanes $\text{RSi}(\text{OCH}_3)_3$ (R = vinyl, phenyl) react with aryl bromides and electron-deficient aryl chlorides according to Equation (12). Also, 2-halopyridines



can be coupled to give 2-aryl pyridines.^[55] The catalyst is formed in situ from $\text{Pd}(\text{OAc})_2$ (3 mol %) and the equimolar amount of bulky imidazolium salt **14b** (also **14c**, isopropyl in place of mesityl). The new catalysts seem to work in reactions of vinyltrimethoxysilane.^[55] As in the majority of papers in this field, no turnover numbers and frequencies (TONs and TOFs) are reported, so comparison with other catalysts is not easily possible.

5.4. Hydrosilylation

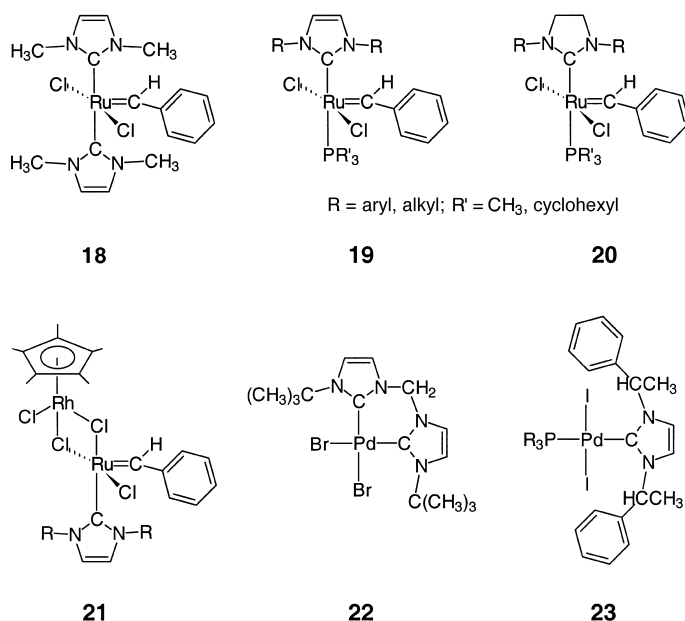
Chiral N-heterocyclic carbenes, their metal complexes, and their successful applications in catalysis appeared in 1996.^[56a] As an example, the hydrosilylation of acetophenone with rhodium catalysts (**16**) was used. The enantiomeric excesses reported at that time (>30%) were subsequently raised



in the Ph.D. thesis work of M. Steinbeck to >70%.^[4b] Simple chiral N-substituents, such as $\text{C}^*\text{H}(\text{CH}_3)\text{C}_6\text{H}_5$, were sufficient to generate significant optical induction into the prochiral substrates. Chelate complexes **17** exhibiting chiral oxazoline building blocks became available in 1998.^[56b] They are made from the free imidazole $\text{C}_3\text{N}_2\text{H}_3\text{R}$ by stepwise treatment with $\text{ClCH}_2\text{C}\equiv\text{N}$, $\text{C}_2\text{H}_5\text{OH}$, and chiral β -aminoalcohols $\text{HOCH}_2\text{C}^*\text{HR}'\text{NH}_2$.

5.5. Olefin Metathesis

Catalytic Heck-type reactions^[44, 47, 57a–c] and a new generation of olefin metathesis catalysts^[57f–n] were reported in 1998/99. On both topics, NHC ligands amply demonstrated their excellence over standard phosphane ligands in homogeneous catalysis. Therefore, these subjects became a major focus of our research.^[7, 57] Typical catalysts with N-heterocyclic ligands for the olefin metathesis are **18–21**, for the Heck coupling **22** and **23**. Catalysts of type **21** (mixed-metal systems) are described in ref. [56].



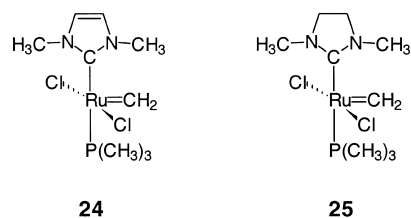
Ring-opening polymerization (ROMP), acyclic diene metathesis (ADMET), and ring-closing metathesis (RCM) are the best understood metathesis varieties as yet. Overviews on the rapid development in this area were given by Grubbs^[58] and Fürstner.^[59] It is clear by now that N-heterocyclic carbenes have made ruthenium the most promising “olefin-metathesis metal”, predominantly because of the high tolerance to functional groups and the mild reaction conditions (normally room temperature).

In an extensive comparative study, Fürstner et al. have adjusted the metathesis catalysts of types **19** and **20** by changing the electronic and steric properties of the NHC ligands.^[59b] They made a comprehensive series of new derivatives, which included those with $\text{Ru}=\text{CHR}$ entities tethered to form a metallacycle, for example, the structurally investigated compound **21**. It was concluded that “No single catalyst outperforms all others in all possible applications”.^[59b] We conclude that the great structural versatility of the catalysts of types **19** and **20** is thus all the more important.

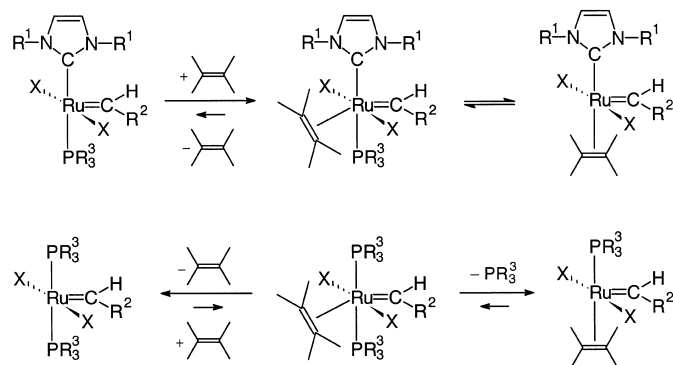
The mixed-ligand olefin metathesis catalysts such as those of types **19** and **20** were first patented^[57k] and then communicated at the XVIIIth International Conference on Organometallic Chemistry in Munich,^[60] before appearing in the journals in 1999.^[57i] Papers by Grubbs^[61] and Nolan's groups^[62] on the same subject followed a little later.^[63] A

series of patents by Grubbs et al. covers some of this work including the synthesis of the corresponding ruthenium NHC catalysts.^[64a–c]

The mixed carbene/phosphane ruthenium catalysts **24** and **25** were subjected to density functional theory (DFT) calculations. They showed low dissociation barriers of the NHC ligands compared to the phosphanes.^[57i] The same overall picture was obtained from palladium(0) species of the type $[(\text{NHC})\text{Pd}^0(\text{PR}_3)]$.^[65]



Ligand-exchange studies, however, revealed that the π -bonding of the olefin (associative mechanism) may be the decisive factor.^[66] Phosphane dissociation is facilitated in $[\text{Ru}(\text{PR}_3)_2\text{Cl}_2(=\text{CHC}_6\text{H}_5)]$, but the resulting 14e-intermediate binds the olefin better in **20**. As seen in Scheme 2, the carbene

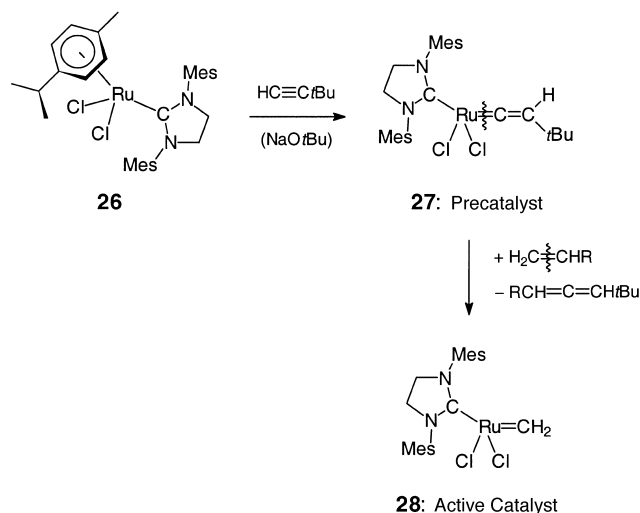


Scheme 2. Equilibria govern the activities of the ruthenium catalysts in olefin metathesis: olefin association versus phosphane dissociation; R^1 = alkyl, aryl; R^2 = C_6H_5 ; R^3 = alkyl, cycloalkyl.

strengthens the olefin binding to the metal, a fact which is thought to account for the excellent activities of catalysts **19**–**21**.^[66] Better olefin association may explain why the bis(NHC) complex **18** is more active than the corresponding bis(phosphane) catalyst $[\text{Ru}(\text{PCy}_3)_2\text{Cl}_2(=\text{CHC}_6\text{H}_5)]$. In the bis(NHC) case, the associated olefin (step 1) could strongly labilize one of the NHC ligands for subsequent dissociation. The mixed-metal catalyst **21** is more ROMP-active than its mononuclear counterpart **19** by an order of magnitude.

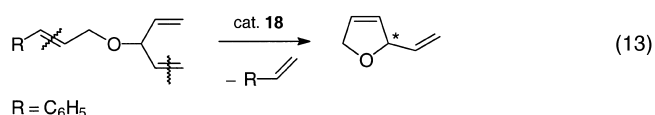
The C–C saturated derivatives **20** were published later in the year 1999.^[67–69] Catalysts **20** exhibit excellent activities, working at monomer:catalyst ratios of up to 1000000:1 for ROMP. However, the stability of type **20** catalysts is clearly lower than that of their C–C unsaturated counterparts. Various applications in the ring-closing metathesis of olefins were reported recently, thus showing the great interest in this field.^[69–71]

As a further exploitation of the outstanding carbene effects, the ruthenium complex **28** was recently generated in situ by Grubbs et al.^[72] and successfully employed in the olefin metathesis. For this purpose, a η^1 -vinylidene precatalyst **27** was generated by a standard method from the *p*-cymene complex **26** and converted into the active catalyst by an olefin metathesis reaction itself (Scheme 3). The major advantages



Scheme 3. Generation of the active CH_2 complex **28** by olefin metathesis of the vinylidene precursor compound **27**.

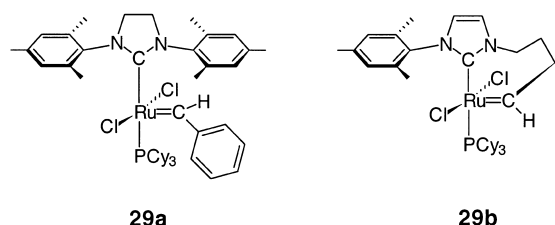
of these catalysts are that they are compatible with functional groups (heteroatoms) and protic solvent systems, and that they work under mild conditions, normally at room temperature. Contributions in the area of olefin metathesis came also from Blechert's group.^[73] In a joint effort, the stereoselective ring-closing metathesis (RCM) following Equation (13) was developed with catalysts **18** and **19**, with the latter ($\text{R} = \text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$; $\text{R}' = \text{cyclo-C}_6\text{H}_{11}$) yielding 40% enantiomeric excess.^[4k, 4n, 73] This results holds promise for an improvement of the desymmetrization of prochiral olefins.



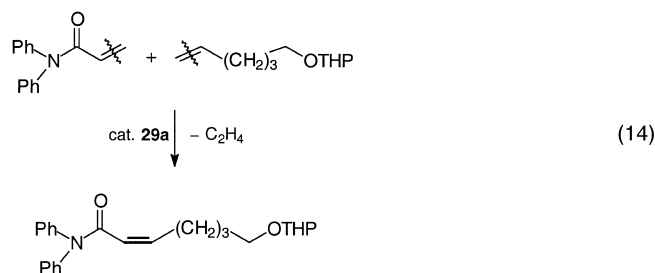
In a similar approach, methylene complexes of type **25** were treated with 1,1-difluorethylene, with the result that the metathesis exchange reaction $\text{L}_x\text{Ru}=\text{CH}_2 + \text{F}_2\text{C}=\text{CH}_2 \rightleftharpoons \text{L}_x\text{Ru}=\text{CF}_2 + \text{H}_2\text{C}=\text{CH}_2$ occurred.^[74] This method is an easy means to generate dihalocarbene metal complexes that are rare in organometallic chemistry.

5.6. Metathesis Cross-Coupling

Not only has the synthesis of trisubstituted and functionalized olefins become possible through the catalyst **29a**,^[75] there is also the cross-metathesis of α,β -saturated amides with terminal olefins, for example, styrene, is also catalyzed by this



compound.^[70] Equation (14) shows one out of numerous examples (THP = tetrahydropyranyl). More electron-rich amides give poorer yields because of carbonyl chelation at the catalytic center. Nevertheless, this is at present the most

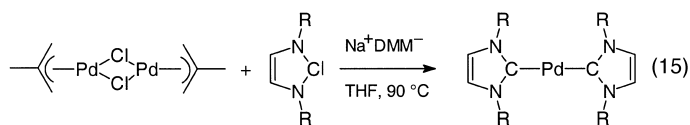


promising approach to a difficult reaction. The chelate congener **29b** of type **19** catalysts combines the steric bulk (*N*-mesityl) with enhanced thermal stability and steric constraints.^[59b]

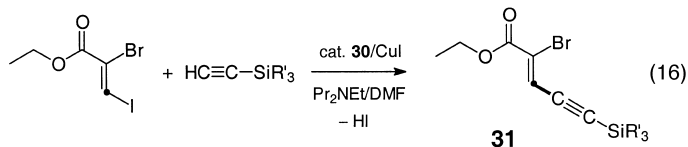
This type of catalyst was recently used to cyclize *N*-allyl-*N*-isopropyl acrylamide by ethylene release (α, ω) in a metathetical approach.^[120] The first product is *N*-isopropyl-3-pyrrolin-2-one. Upon warming, a radical reaction with the same catalyst leads to a chlorinated product.^[120]

5.7. Sonogashira Coupling

The palladium(0) species **30**, which is active in the Heck and Suzuki C–C-coupling,^[76] can also be employed to furnish a Sonogashira-type coupling to make the bromo-eneyne **31**, a common building block of natural products [Eq. (16)]. The



DMM[−] = dimethylmalonate; R = *t*-C₄H₉

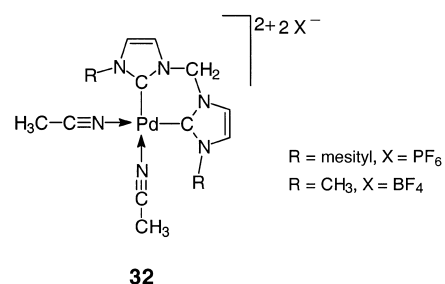


analogy with the standard catalyst [Pd{P(C₆H₅)₃}₄] was noted by the authors who, at the same time, presented a new, simple synthesis of Pd⁰ bis(carbene) complexes: (π -allyl)pallad-

ium(II) chloride is treated with the free carbene under reducing conditions [Eq. (15)]. Copper-free conditions were reported for the Sonogashira coupling of aryl bromides with alkynylsilanes on Pd(OAc)₂/**14b** or **14d**.^[121]

5.8. Ethylene/Carbon Monoxide Copolymerization

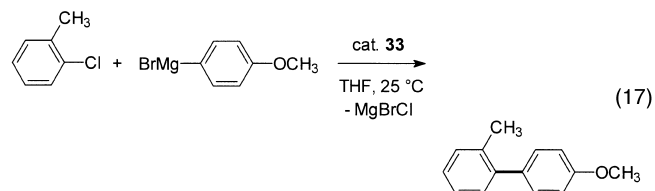
Yet another catalytic application was found in 1999: dicationic palladium(II) NHC complexes such as **32** catalyze the copolymerization of C₂H₄ and CO to give high molecular



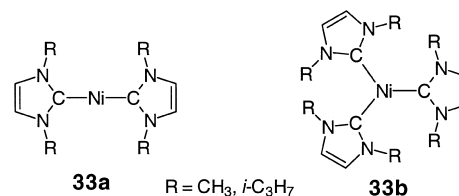
weight, strictly alternating poly(C₂H₄-alt-CO) under mild conditions and low pressure.^[77] Polyketones play a considerable role in numerous technical applications, particularly in the car industries.

5.9. Kumada Coupling (Grignard Cross-Coupling)

A promising entry into the Grignard cross-coupling of aryl chlorides as sketched in Equation (17) was opened by NHC catalysts of nickel.^[78] Generated in situ from [Ni(acac)₂] and



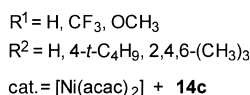
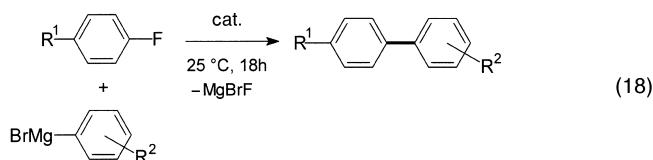
imidazolium salts, the catalysts—very likely zero-valent nickel species such as **33a, b**—effect the C–C coupling even at room temperature (3 mol % Ni). All previous catalysts required



much higher temperatures, with the result that they suffer from insufficient selectivity because of the formation of numerous side products. The related palladium(0) catalysts mentioned by Nolan et al.^[79] are less active than the nickel(0)

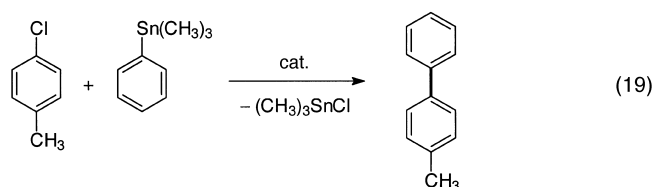
systems; they require higher temperatures, typically around 80 °C.

The first case of catalytic C–F bond activation in conjunction with selective C–C bond formation was observed with NHC–nickel catalysts.^[80] Once again, a sterically demanding carbene **14c**, was successful and simply generated in situ from [Ni(acac)₂] and the azolium salt [Eq. (18)]. The yields of the desired heterocoupling products were as high as 97 % (R¹ = CF₃). Both the product selectivity and the Hammett correlation suggest a polar reaction and disfavor the radical pathways seen to participate when NiCl₂ alone is used as a coupling reagent.^[80]



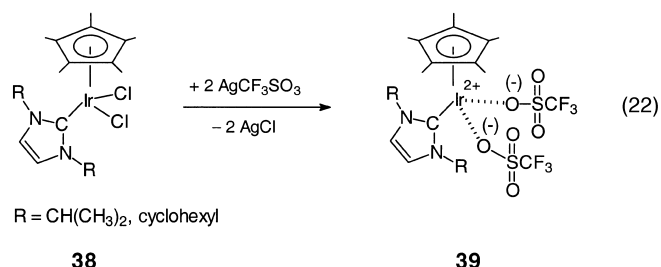
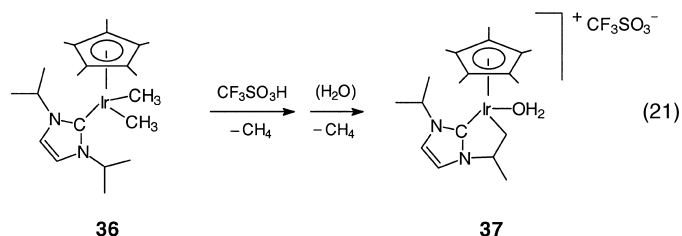
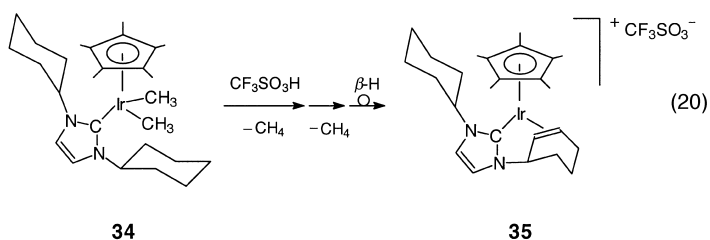
5.10. Stille Coupling

Another common type of C–C coupling, named after John Stille, works with catalysts that were generated from Pd(OAc)₂ and imidazolium salts.^[81] Equation (19) shows a typical example, which works well in 1,4-dioxane at 100 °C (12 h) in the presence of tetrabutylammonium chloride.

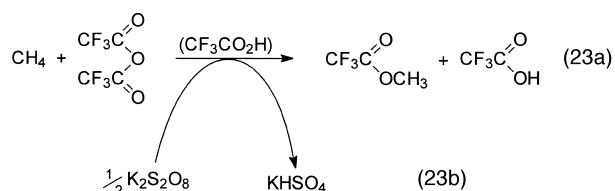


5.11. C–H Activation

Certain NHC complexes of iridium have a strong tendency to undergo C–H activation. For example, the dimethyl iridium(i) species **34** undergoes loss of methane under protolytic conditions, and forms the internal π -olefin complex **35** in a stepwise manner and in high yields by β -H migration [Eq. (20)].^[82] The related process occurs with the isopropyl derivative **36** [Eq. (21)].^[82] However, the stable dicationic **39** can be generated without CH activation from the dichloro complex (**38**) instead of the dimethyl precursor compound [Eq. (22)].^[82] This story tells us that 1) chelate structures of NHC–metal complexes can spontaneously occur by C–H activation, and 2) the latter reaction is principally feasible with NHC–metal catalysts.



As a matter of fact, a new approach to the activation of the greenhouse gas methane was opened by virtue of the NHC–palladium complex **11b** (*t*-C₄H₉ in place of CH₃): Trifluoroacetic anhydride yielded the methyl ester upon treatment with methane in the presence of potassium peroxodisulfate^[83, 84] according to Equations (23a) and (23b). Remarkable are the



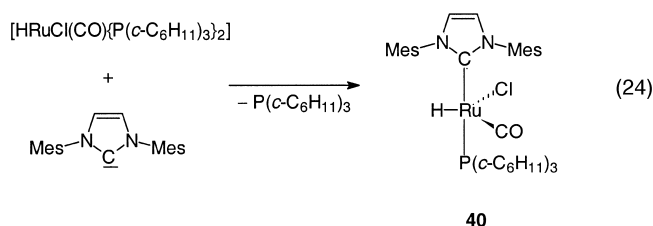
relatively mild reaction conditions: 20–30 bar CH₄, 80–90 °C. The peroxodisulfate provides the redox equivalents necessary to balance the conversion CH₄ → H⁺ + CH₃⁺ + 2 e[−]/O₂^{2−} + 2 e[−] → 2 O^{2−}. Neither the Periana (Pt) nor the Sheldon system (Pd) gives any methane activation under such conditions.

5.12. Hydrogenation, Hydroformylation

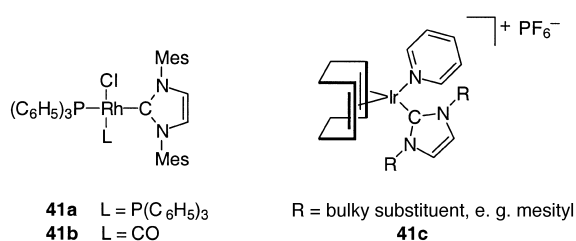
These olefin functionalization reactions work with rhodium(i) catalysts of type **16**, as mentioned in previous reviews^[7, 56] based on the Ph.D. theses of M. Steinbeck,^[4b] J. Fischer,^[4d] and C. Köcher.^[4g, 29] Detailed investigations are

required in this promising, industrially relevant area. The concept of two-phase catalysis has plenty of potential here, especially since successes were achieved with this principle in the industrial Ruhrchemie/Rhône-Poulenc process.^[85, 86] Water-soluble NHC–metal complexes are known, too.^[30]

Recent reports predict a great future of NHC catalysts in alkene hydrogenation: Using sterically hindered ligands, the Nolan group achieved TONs up to 2.4×10^5 at only 4 bar hydrogen pressure at 100 °C for the substrate 1-hexene.^[87] However, the ruthenium(II) catalysts tested work well only at elevated temperatures but not under the mild conditions typical of the classical Wilkinson (Rh) catalyst. Also, the replacement of phosphane by the carbene [Eq. (24)] does not dramatically improve the catalyst's activity. The 14e intermediate $[\text{HRu}(\text{CO})(\text{Cl})\text{L}]$ is thought to be the active species, the formation of which is enhanced by addition of $\text{HBF}_4 \cdot \text{O}(\text{C}_2\text{H}_5)_2$.^[87] Catalyst **40** has a distorted trigonal-pyramidal structure in the solid state.^[87]



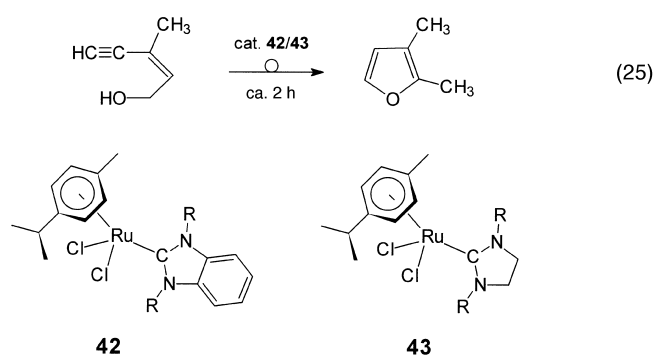
Based on our results,^[29] vinylarenes were subjected to hydroformylation with NHC–rhodium catalysts. High selectivities were obtained for the branched isomer,^[88] possible candidates in the synthesis of important pharmaceuticals, such as ibuprofen. Branched-to-linear ratios of up to 97:3 were obtained with styrene and some of its derivatives in the presence of square-planar catalysts **41a** or **41b** made by ligand exchange from Wilkinson's catalyst $[\text{RhCl}(\text{P}(\text{C}_6\text{H}_5)_3)_3]$. Unfortunately, the catalytic activities are still low ($\text{TOF} < 10 \text{ h}^{-1}$), in accord with earlier reports on catalyst **16**.^[4g, 29]



Cationic NHC–iridium(III) catalysts of type **41c** were used in olefin hydrogenation^[89] and in transfer hydrogenation with ketones.^[90] The catalyst stability is at the expense of activity in these cases. However, increased hydrogen pressure at 50 °C gives acceptable results.^[89]

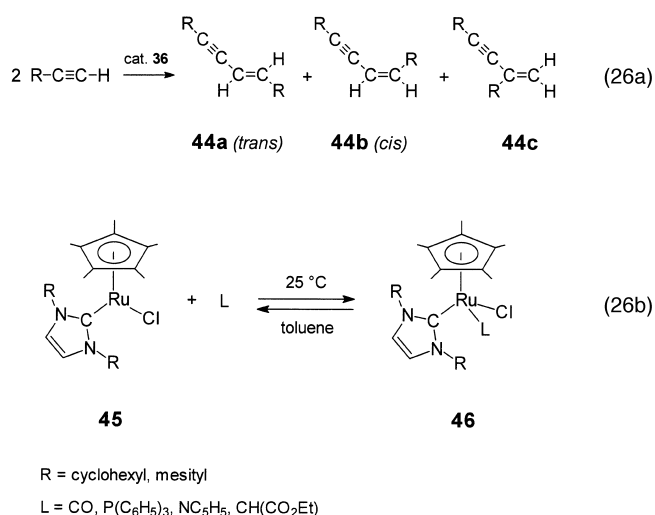
5.13. Furan Synthesis and Alkyne Coupling

A quasi-catalytic furan synthesis by the rearrangement reaction following Equation (25) was reported by Dixneuf



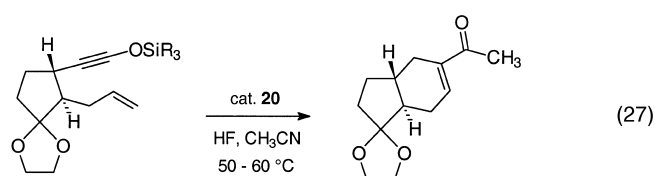
et al.^[91] The catalyst **42** is a benzimidazolin-2-ylidene complex of ruthenium.^[91a] Yields of around 80% were reported (1 mol % cat., 80 °C, 25 h). In a subsequent paper, the improved catalyst **43** was used.^[91b]

An alkyne coupling reaction following Equation (26a) was described by Herrmann and Baratta.^[27a] Once again, ruthenium is required as the mediating metal. The NHC complex **45** used for this purpose^[27b] associates 2e ligands such as phosphanes and carbenes to form tetracoordinate adducts **46**, [Eq. (26b)]. The π addition of alkynes clearly facilitates the



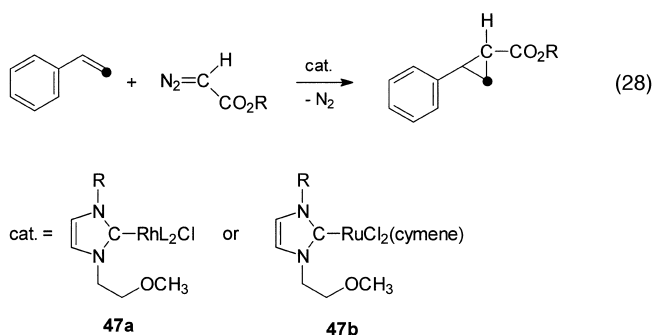
consecutive C–C-coupling. Conversions as high as quantitative were achieved with $\text{R} = \text{C}_6\text{H}_5$, $\text{C}_6\text{H}_4\text{-}p\text{-CH}_3$, SiMe_3 within 5–10 min. In most cases, the *trans*-coupling product **44a** dominated, with the exception of $\text{R} = \text{SiMe}_3$ where the α -olefin **44c** was formed >92%. Maximum turnovers of $\text{TOF} = 10320$ ($\text{TON} = 860$) were reported so far.^[27a]

Highly functionalized enones are accessible from readily available acyclic precursor compounds when NHC–ruthenium metathesis catalysts such as **20** ($\text{R} = \text{mesityl}$) are applied. Combined with efficient protodesilylations, this process gives conversions up to 98% at 60 °C, starting from appropriate siloxyalkynes.^[126] Equation (27) represents an excellent example of an alkene–siloxyalkyne metathesis.



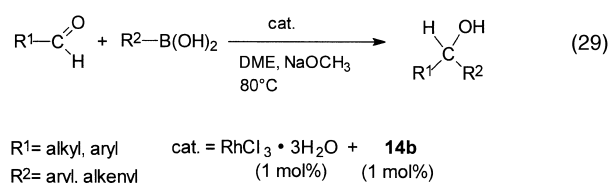
5.14. Olefin Cyclopropanation

Rhodium(i) and ruthenium(ii) complexes **47** containing NHCs with hemilabile, dangling ether moieties were successfully used as catalysts for the cyclopropanation of olefins with diazoalkanes, [Eq. (28)].^[92] This reaction is of industrial use in the synthesis of insecticides.



5.15. Arylation and Alkenylation of Aldehydes

A convenient, user-friendly method for the addition of aryl or alkenyl boronic acids to aldehydes employs a catalyst formed in situ from RhCl₃ · 3H₂O, the bulky imidazolium salt **14b**, and inexpensive aqueous bases.^[93] The addition is chemoselective for aldehydes and compatible with many functional groups in both reaction partners. Secondary aldehydes—possibly asymmetric varieties in the future—are thus formed according to Equation (29) in good to excellent yields.^[93]



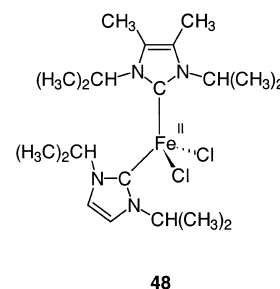
5.16. Reduction of Aryl Halides

Dehalogenation of aryl halides was performed when nickel(0) catalysts (3 mol %) of bulky N-heterocyclic carbenes were used in the presence of β-hydrogen containing alkoxides, with the latter acting as reducing agents.^[128] Most efficient once again was the carbene derived from the imidazolium salt **14b** by in situ deprotonation by the alkoxide (normally

NaOiC₃H₇). Mild reaction conditions (THF, 65 °C, 1–3 h) are convincing indications that this new way of replacing halides (F, Cl, Br, I) by hydrogen can find practical use through further improvement.

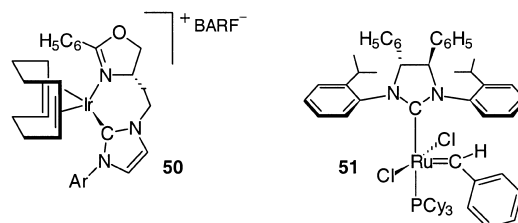
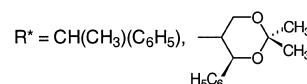
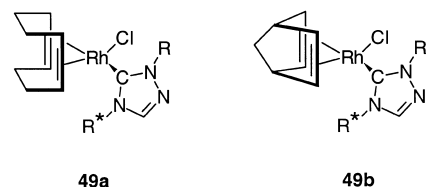
5.17. Atom-Transfer Radical Polymerization

Styrene and methyl methacrylate undergo atom transfer radical polymerization (ATRP) in the presence of catalysts possessing donating NHC ligands. Thus, the tetrahedral iron(ii) complex **48**, reported by Grubbs et al.,^[94] works at 85 °C for styrene to provide a polymer with low polydispersities (*M_w/M_n* ≈ 1.1). ATRP is a method to control free-radical polymerizations. Compound **48** gives the highest polymerization rates seen for ATRP in organic solvents to date.^[94]



5.18. Asymmetric Catalysis

Apart from a few examples, stereoselective synthesis has to date not been generally investigated with NHC catalysts. The number of reported successes in correspondingly small. In the Enders' group in particular, however, triazolynylidene ligands have developed a convincing potential.^[95] Chiral catalysts such as **49** and **50** (BARF = tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate) gave moderate optical inductions up to 44 %

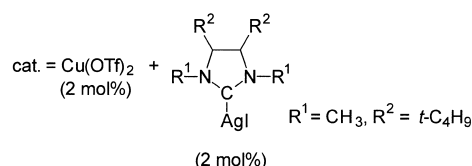
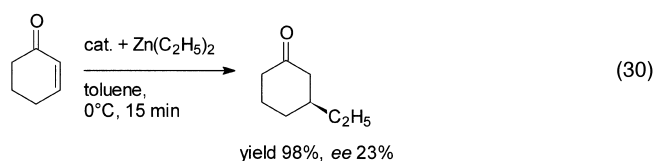


in hydrosilylation reactions.^[95a,d, 96] A number of optically pure, both soluble and immobilized rhodium, ruthenium, and palladium complexes were synthesized and characterized.^[95] Catalyst **51** was used for the desymmetrization of *meso*

compounds. For example the asymmetric catalyst effects the conversion of 4-allyloxy-3,5-dimethyl-2,5-heptadiene into (2*S*)-((2*Z*)-buten-2-yl)-3-methyl-2,5-dihydrofuran in 90% enantiomeric excess.^[120]

Good to excellent stereoselectivities in the hydrogenation especially of trisubstituted alkenes (25 °C, 50 bar H₂) were obtained by virtue of the NHC-chelate iridium(III) catalyst **50**.^[123] The cationic catalyst is modeled after the basic structure of **41c**.^[90] This was the first report of high optical induction using electron-rich carbene ligands in catalytic processes.

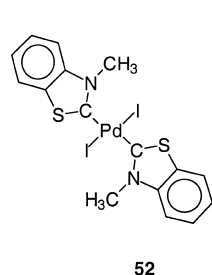
Chiral silver(I) diaminocarbenes act as carbene transfer agents to copper salts. The products catalyze the addition of diethylzinc to cyclohexanone^[97] according to Equation (30). The optical yields are certainly subject to further improvement but the easy generation of the catalyst is striking indeed.



6. Ionic Liquid Effects

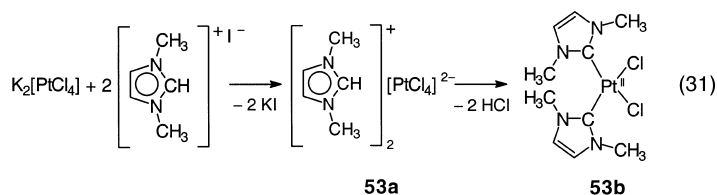
Great progress in catalytic C–C coupling reactions was recently made with non-aqueous ionic liquids (“NAIL”).^[98] As demonstrated for the Heck coupling of aryl halides, molten tetraalkylammonium halides (particularly [N(C₄H₉)₄][Br]) improved both the stability and activity of almost every known palladium catalyst system compared to standard solvents such as DMF, *N,N*-dimethyl acetamide, or 1-methyl 2-pyrrolidone.^[98b] Remarkably, the yield with the NHC catalysts **10** improves from 20% to >99% for the coupling of bromobenzene with styrene. Effects of similar magnitude were reported for low reactive chloroarenes.^[98b]

Ionic solvents are relatively expensive. However, they can be recycled, without loss of catalyst. In the mechanistic considerations, anionic catalyst species of type [Br–Pd⁰–Ligand][–] are invoked, at least for the NHC- and palladacycle catalyst systems Pd^{II}, albeit Pd^{II}/Pd^{IV} equilibria cannot be ruled out.^[98b]

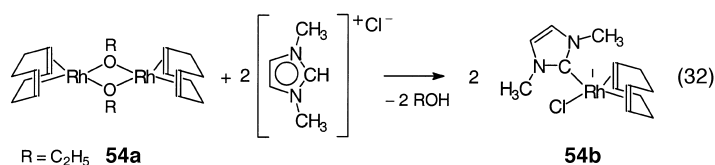


The ionic-liquid concept^[98] was taken up by the Italian group of Calò.^[99, 100] They used related palladium complexes of benzothiazole carbene ligands **52**^[99b] in a melt of tetra(*n*-butyl)ammonium salts to carry out the coupling of aryl bromides with 3-hydroxy-2-methylene alkanones. β -Aryl ketones are thus formed in good yields.

Imidazolium salts are among the best investigated ionic liquids. Their beneficial effects in catalytic processes may in part originate from their easy conversion into NHC-metal complexes, since coligands of reasonable basicity are known to induce deprotonation.^[24, 29] Reactions following Equation (31) to convert the imidazolium metallate **53a** into the



NHC complex **53b** may then occur under a pseudo “ionic liquid effect”. A Russian report is indicative of the chemistry following Equation (31) but the product was not unambiguously characterized because of concomitant decomposition reactions.^[101] Similarly, the alkoxy rhodium complex **54a** undergoes spontaneous formation of the NHC derivative **54b** [Eq. (32)] a reaction which is now a standard synthesis^[19].

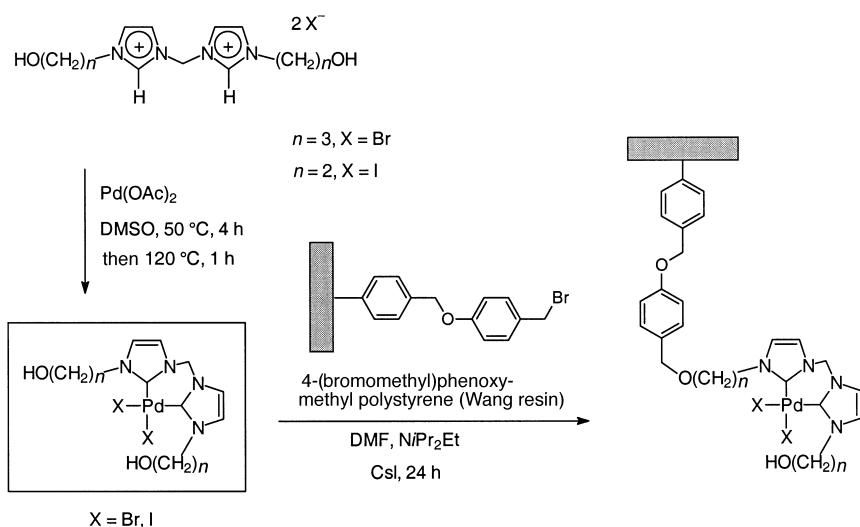
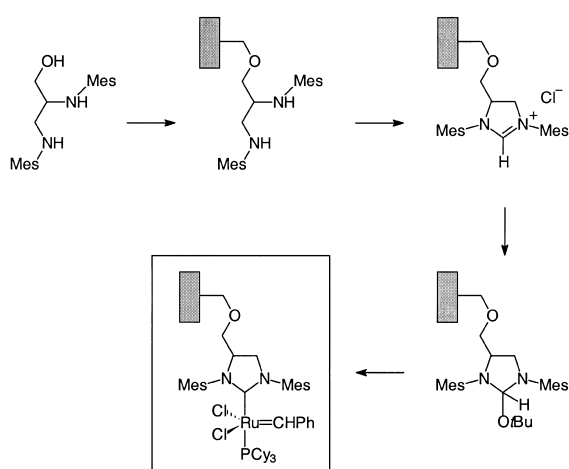
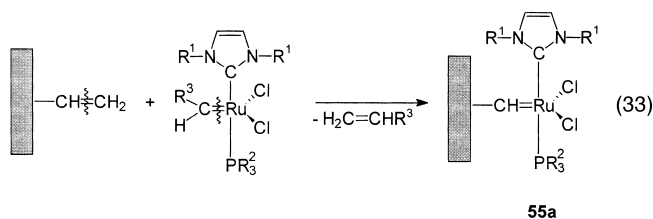


7. Avoiding Catalyst Leaching

Polymer-supported NHC catalysts were published in 2000: Good results in the Heck coupling reactions were achieved with polymers on the basis of the Wang resin (4-bromomethyl)phenoxyethylpolystyrene. Hardly any catalyst leaching was observed, which supported earlier proposals that the NHCs are strongly bound to the catalyst metal center.^[7] The methodology is outlined in Scheme 4 and described in full detail in refs. ^[41, 65]

An alternative strategy was pursued by Blechert et al. to obtain a polymer-supported olefin metathesis catalyst. In this case, the polymer-anchored ligand precursor was built up first and then treated with the catalyst metal compound. Scheme 5 outlines this straightforward methodology.^[102] Excellent results were obtained in the ring-closing metathesis and the cross-metathesis, for example, yne–ene metathesis.^[102] Yao developed a soluble poly(ethylene glycol) (PEG) bound polymer catalyst of type **18** which is immobilized through the phenylalkylidene moiety to a PEG support.^[103]

Four consecutive ring-closing metathesis steps were achieved by Barrett et al. with the help of recyclable catalysts of type **55**.^[104] Here, the classical carbene that initiates the metathesis is itself anchored to the vinylated polystyrene resin by a metathetical step as shown in Equation (33). This catalyst is more efficient in olefin metathesis, especially in RCM, than the congener derived from the bis(phosphane) ruthenium complex [(PR₃)₂RuCl₂(=CHR³)]. The working principle of

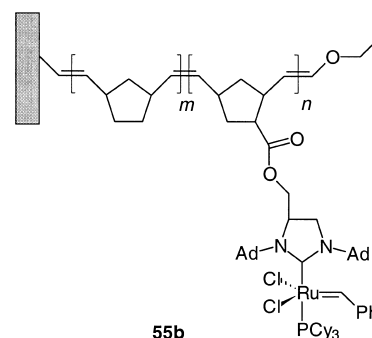

 Scheme 4. Immobilization of a NHC palladium catalyst according to Herrmann et al.^[65]

 Scheme 5. Immobilization of a NHC ruthenium catalyst according to Blechert et al.^[102]


$\text{R}^1 = \text{mesityl}; \text{R}^2 = \text{c-C}_6\text{H}_{11}; \text{R}^3 = \text{C}_6\text{H}_5$

this new type of “boomerang” catalyst is based on the reversible release of the metallacarbene moiety into the solution phase from the resin, and recovery by the support after reaction. The ruthenium contamination of the products is thus minimized. Beyond that, catalyst recovery and recyclability are improved.^[104]

An elegant approach to immobilized olefin-metathesis catalysts was reported by Buchmeister et al.^[125] They prepared monolithic materials exhibiting a particle diameter of $1.5 \pm 0.5 \mu\text{m}$, by the metathetic copolymerization of appropriate olefins. The monolithic carrier is then functionalized

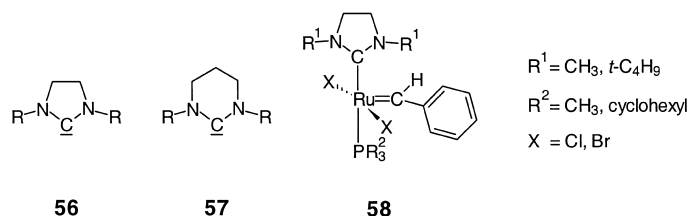
by “living” NHC-ruthenium termini (from amidazolium precursor and $[\text{Cl}_2\text{Ru}(\text{PCy}_3)_2=\text{CHC}_6\text{H}_5]$). The catalyst **55b** (Ad = adamantyl) thus formed shows high activities in both the ring-closing and ring-opening metathesis, with *cis/trans* ratios in the polymeric products that correspond exactly to what has been seen in homogeneous catalysis. The lack of any microporosity in the catalysts **55b** minimizes diffusion effects to a large extent, thus giving high turnover frequencies often beyond those of homogeneous catalysts.



An alternative concept—immobilization of olefin metathesis NHC-catalysts on a monolithic material prepared by a sol–gel technique—was presented by Hoveyda et al.^[127] They made ruthenium-containing glass pellets that efficiently promote olefin metathesis reactions. The catalysts are robust and stable in air.

8. 2,3-Dihydro-1H-imidazol-2-ylidenes

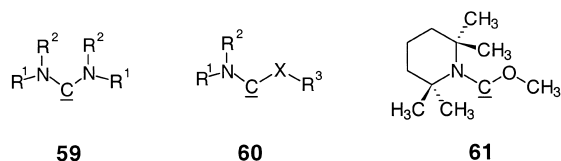
C–C saturated N-heterocyclic carbenes are expected to be yet stronger σ -donor ligands than their C–C unsaturated counterparts. While the five- and six-membered compounds **56** and **57**, respectively, have been documented in metal



complexes for quite some time.^[105] Thus, the examples **58** were independently reported by the research groups of Grubbs^[68] and Herrmann,^[67] and showed that the activity for the olefin metathesis is—with the reactions investigated—higher than that of the C–C unsaturated analogues. However, the catalyst stability seems generally lower.

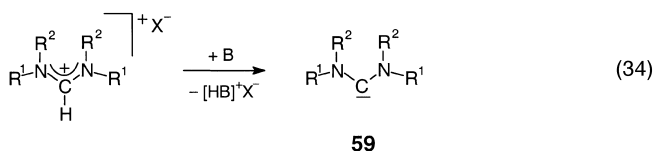
9. Acyclic Bis(amino)carbenes

A new approach in catalysis is the use of the “open-chained” bis(amino)carbenes **59**–**61**. They are accessible from the corresponding formamidinium salts according to

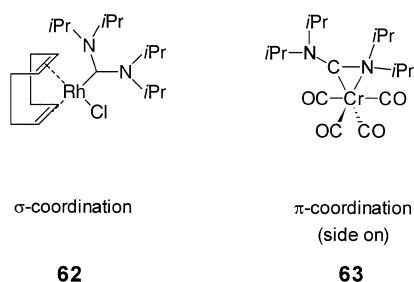


R^1, R^2 = alkyl, aryl; R^3 = aryl; X = O, S

Equation (34), as shown by Alder et al.^[107] It was found that the free carbenes are stable for a number of substituents R^1 and R^2 , with the most investigated members of **59** carrying



two diisopropylamino or two piperidyl substituents.^[108] Neutral and anionic deprotonation agents can be used, preferentially $\text{Li}[\text{N}(\text{iC}_3\text{H}_7)_2]$ or $\text{K}[\text{N}(\text{SiMe}_3)_2]$ in liquid ammonia, to generate this specific subgroup of N-functionalized carbenes. Several metal complexes were synthesized with these ligands, for example **62**.^[106, 108] The stable aminooxy- and aminothio-carbenes such as **60** described recently by Alder et al.^[107b] are close to the classical Fischer-type carbene complexes.

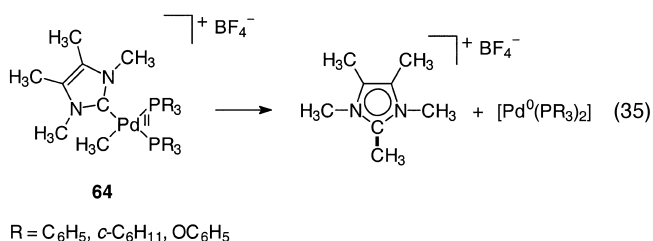


It is worth of mention that bis(amino)carbenes can (side-on) coordinate to transition metals. For example, the tetracarbonylchromium(0) complex **63** has a $\eta^2(\text{C}, \text{N})$ -coordination, with bond lengths of 192.0(1) pm for the carbene–chromium bond and 220.7(1) pm for the nitrogen–chromium bond. Accordingly, the respective C–N bonds differ by around 15 pm.^[34] This effect may very well stabilize the under-coordinated “resting state” of N-heterocyclic carbene catalysts.

10. Theoretical Studies

The bonding theory of N-heterocyclic carbenes with regard to their cyclic structure and their metal bonding has been the subject of theoretical studies that are covered in previous review articles.^[7] Experimental and theoretical charge-density studies revealed that free NHCs have somewhat less π -electron delocalization than in their metal complexes.^[34] Acyclic bis(amino)carbenes (e.g., **59**) donate significantly more electron density to metals than their cyclic counterparts.^[108a] Here, the nitrogen lone pairs can participate in intramolecular coordination to the metal.^[34] Recent density functional theory (DFT) studies predict that oxidative addition of imidazolium salts to platinum(0) is an exothermic process.^[109] This result is consistent with the experimental finding that a hydridoplatinum(II) NHC complex is thus formed.

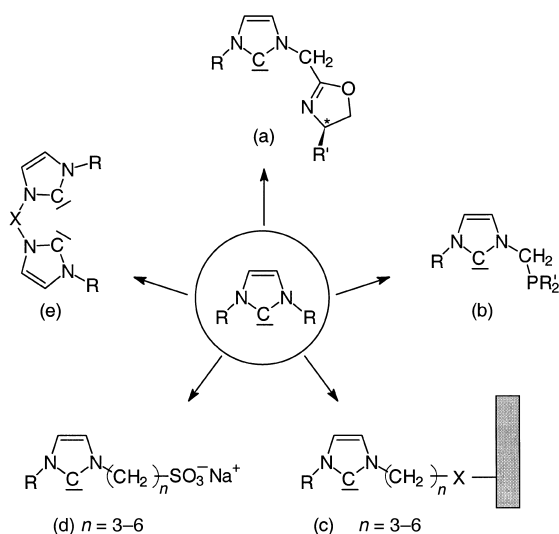
Kinetic and DFT studies on alkyl-carbene elimination from NHC–palladium(II) complexes revealed a new type of reductive elimination with implications for catalysis.^[110] Elimination of methylimidazolium cations from **64** [Eq. (35)] proceeds in a concerted way and suggests similarities in the reactivity of M–R and M–N(NHC) bonds. This finding once again highlights the principal differences between conventional metal–carbenes $[\text{L}_x\text{M}=\text{CR}^1\text{R}^2]$ and N-heterocyclic carbenes.^[110]



11. Perspectives

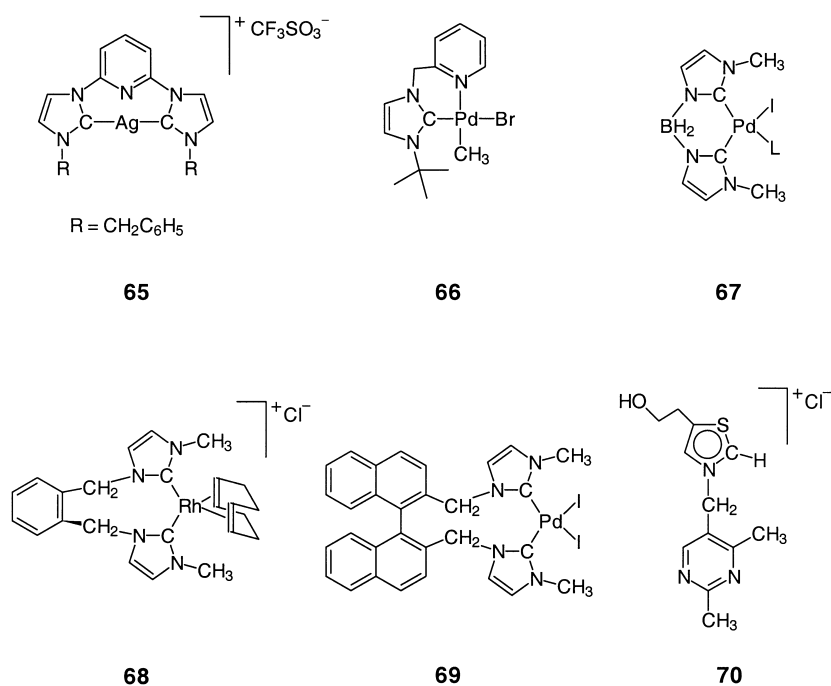
What have we learned from the foregoing discussion? N-Heterocyclic carbenes (NHCs) clearly are not just “phosphane mimics” as they are sometimes called in the literature. They are more than that, they are versatile and easy-to-make ligands with great potential in homogeneous catalysis. There is increasing experimental evidence that NHC–metal catalysts surpass their phosphane congeners in both activity and scope of application. The most convincing and best studied example so far has been olefin metathesis, for which reaction ruthenium–NHC catalysts were exploited independently by two research groups. Here, it became evident that organophosphanes—ubiquitous standard ligands in organometallic chemistry—give poorer catalytic performance than NHC ligands in structurally analogous catalysts. The NHC–ruthenium complexes are the most active catalysts of olefin metathesis known to date. They tolerate functional groups, and work at ambient temperature. NHCs strongly bind to typical catalyst metals, but do not undergo ligand dissociation, at least in the hitherto investigated cases.

Structural versatility is a great strength of N-heterocyclic carbenes (Scheme 6): chirality (a), functionalization (b), immobilization (c), water solubility (d), and chelate effects (e) can be achieved by easy means. All these varieties have principally been verified, and stable transition metal complexes were described in all cases.^[4, 7]



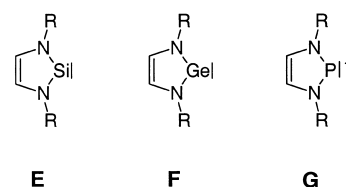
Scheme 6. The versatility of ylidenes derived from imidazolium compounds.

Numerous new varieties of NHC-metal complexes were reported within a short period of time, among them the first alkaline earth complexes,^[33] the silver salt **65** with its strained structure,^[111] the pyridyl-NHC palladium chelate **66**,^[112] the nine-membered rhodium complex **68**,^[29] and the eleven-membered chiral palladium complex **69**.^[113] The electronic effects in chelating NHC-metal complexes may also be adjusted for certain purposes by changing the bridging groups.

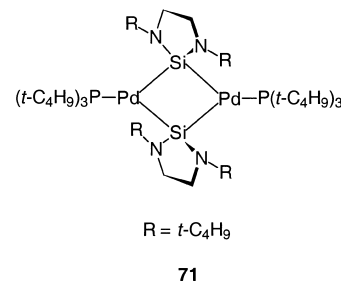


For example, the formally anionic BH_2^- group in complex **67** can replace the isoelectronic standard CH_2 moiety, thus changing the charge of the metal.

Some of the ionic-liquid effects in organometallic catalysis are likely to arise from NHC catalysts, be it as free carbenes or as their metal complexes; both can be readily formed in situ from azolium salts. It is also reasonable to assume in biological systems similar phenomena occur when the ubiquitous imidazolium groups interact with metal ions. We know from the foregoing discussion that NHC ligands are compatible with literally any kind of metal in low and high oxidation states. The naturally occurring thiazolium salt thiamine **70**, the coenzyme of vitamin B₁, catalyzes the decarboxylation of pyruvate, with the deprotonated ylide form of **70** known to be the active catalyst.^[114] The biochemistry of NHC-metal complexation lies ahead of us like an uncharted sea.^[131] This is also true for the chemistry of the homologous and isoelectronic congeners **E**, **F**, and **G** metal compounds of which have

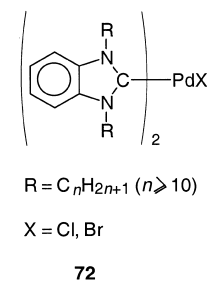


been described in some detail,^[22, 115] including the C-C saturated derivatives of the silylenes and germylenes. Now that the heavier congeners of carbenes are available, this field is also ready to be developed in organometallic catalysis. As a matter of fact, the μ -silylene palladium complex **71** has just



been made and structurally characterized.^[116a] It dissociates in solution to form low-coordinate mononuclear palladium species. The analogous compound of the C-C unsaturated silylene was reported, and has moderate activity in the Suzuki coupling (aryl bromides).^[116b]

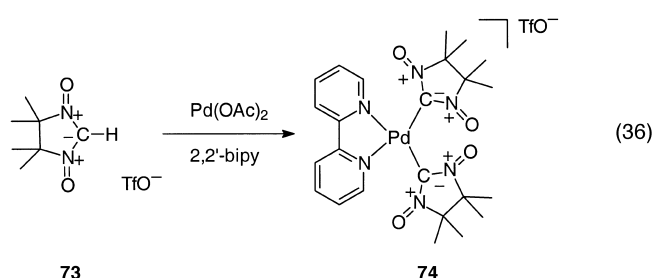
Beyond catalysis, N-heterocyclic carbenes are going to gain relevance in materials science. For example, Liu et al. just reported on the first thermally stable liquid crystals based on NHC-palladium complexes such as **72**.^[117] The arrangement of this type of rodlike molecule results in



the preferential formation of a monolayered lamellar structure. The mesophases of **72** and related compounds have a mosaic texture. The new liquid crystalline phases are thermally stable up to the isotropic temperatures without decomposition. Once again, the ease of preparation, the thermal stability, and the structural versatility are unique features, as in catalysis.

Addendum: Dinitroxide Carbenes

A peculiar class of N-heterocyclic carbenes was recently described by Weiss et al.^[130] Although unstable in the free state, the nitroxide carbene **73** could coordinate to a palladium(II) center, to form the cationic, diamagnetic complex **74** [Eq. (36)]. These carbenes can be regarded as



nitronyl–nitrosonium systems. A reversed-polarity singlet structure is stabilized here, with the carbene acting as π -donor and as π -acceptor ligand at the same time (“Autoumpolung” concept). The Pd–C bond of 197.7(4) pm (X-ray diffraction study) is in the typical range as in related NHC complexes. The variable electronic nature of the dinitroxide carbenes predisposes them as electronically flexible ligands. Complexes of Ag(I), Au(I), and Hg(II) were also obtained.^[130]

The work in my research group is performed by many skillful and innovative Diploma, Ph.D., and Postdoctoral students. Their dedication and spirit has opened a new, fascinating area of organometallic chemistry and catalysis. The results once again demonstrate that science is an undertaking for our young generation. I am grateful that I could always rely on my research students who organized their work so efficiently that I was able to serve to my university as President at the same time. Jörg Fridgen is acknowledged for the flawless preparation of the formulae, equations, and schemes presented in the above text. I thank Dr. Karl Öfele, our pioneer of NHC coordination chemistry, for excellent advice over the many years we shared common research interests in the Anorganisch-chemisches Institut of Technische Universität München.

Received: July 3, 2001 [A 483]
Addendum: February 6, 2002

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Flüchten, Mitmachen, Vergessen

Chemiker und Biochemiker in der NS-Zeit *



Fritz Haber

...My decision to request my resignation comes from the contrasts between the tradition with regard to research, in which I have lived so far, and to the altered views which you, Herr Minister, and your ministry, represent as champions of the huge current national movement. My tradition in my scientific position requires that in the selection of workers I consider only their technical abilities and their character without asking about their racial origins.

Fritz Haber, April 30, 1933

...We also recognize the overwhelming contribution to the fundamentals of modern chemistry that can be attributed to the Western civilizations that have given the world a Scheele and a Berzelius, a Lavoisier and a Pasteur, an Avogadro and a Cannizarro, a Liebig and a Wöhler. To ensure the survival of their blood, and the further development of this culture the peoples of Europe are under arms, just as those of the old east Asian cultural area are for theirs. We think of the men in whose hands our combined fates lie, the Duce, Tenno, and our Führer, three times Sieg Heil.

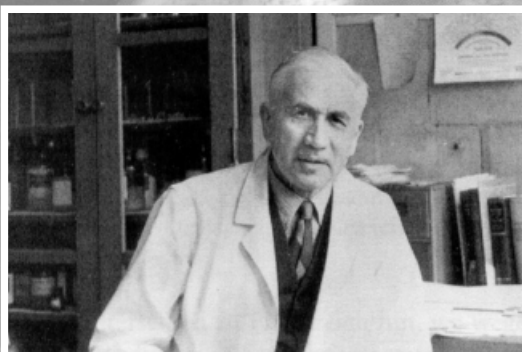
Richard Kuhn, December 5, 1942



Richard Kuhn

Forgiveness is not my responsibility, but that of a higher power. Our duty is to keep the memory of this horror alive and thus to prevent future generations from living through it again. That is, I think the most important responsibility of German researchers and educators today.

Otto Meyerhof, April 28, 1947



Otto Meyerhof

* The book *Flüchten, Mitmachen, Vergessen: Chemiker und Biochemiker in der NS-Zeit*, is published by Wiley-VCH, its title can be translated as *Flee, Collaborate, Forget: Chemists and Biochemists in the National Socialist Era*.

Chemists and Biochemists during the National Socialist Era

Ute Deichmann*

Chemistry and biochemistry in Germany was notably affected by the dismissal and emigration of Jewish scientists. The expulsion of Jewish scientists aided to significantly reduce the international regard for German science, particularly in biochemistry, physical chemistry, and quantum chemistry, after 1945. In most cases

remaining scientists adjusted quickly after 1933 to the new political circumstances, with a few exceptions. A number of them even actively supported the politics of National Socialism. This fact as well as the common stance to forget the 12 years of National Socialist rule complicated the exchange of international scientific

knowledge after 1945 and delayed affiliation of the weakened fields of research to the level of international research.

Keywords: antisemitism • emigration
• history of chemistry • science policy

Introduction

In 1938 Arthur Schleede, Professor of Inorganic Chemistry at the Technische Hochschule in Berlin, a member of the NSDAP since 1933, complained in a letter to the president of the Deutsche Chemische Gesellschaft (the German Chemical Society), Richard Kuhn, that five years after the National Socialists had come to power it was still possible for a number of Jewish chemists to appear as co-editors of German scientific journals:

"Irrespective of the true admiration for the actual achievements of other nations we must assume a German attitude in the presentation of our German journals. Not without reason does foreign journalism regard German science as a stronghold of reactionism, for five years after the awakening of the German nation, it was still possible for Jews to appear as co-editors on the title pages of German journals, with their names in full and at times even with their current addresses. No matter whether Jew with recognized achievements, such as Willstätter, or Jew with none, such as Paneth (...). From the perspective of foreign countries this attitude of 'objective science' gives rise to the impression of criticism of the fundamentals of National Socialism by the German intelligentsia, yet it is of particular importance that it is German chemists who have made a considerable contribution to the worldwide renown of the German nation."^[1]

It is worth noting that at this time, Friedrich (Fritz) Paneth had already received international recognition through his work in the areas of radiochemistry (in cooperation with Georg von Hevesy) and the proof of the existence of free alkyl radicals by using radiomarkers (in cooperation with Hofeditz). There is no record of a response by Kuhn to Schleede's letter. Shortly afterwards, however, Paneth, who was living in exile in London, received a letter from the publishers of the *Zeitschrift für Anorganische und Allgemeine Chemie*, Wilhelm Biltz and Gustav Tamann, that informed him that in future the list of collaborators on the title page of the journal would be omitted since *"this list no longer corresponds to the current status of our journal."*^[2]

Schleede's letter demonstrates two characteristic attitudes of German chemists and biochemists in Germany after 1933: on the one hand almost all accepted a new definition of that which was to be regarded as the "German viewpoint". In agreement with the Nuremberg Rassengesetzen (Race Laws) of 1935 not only were Jews no longer regarded as Germans, but they were to be excluded from all scientific activities in Germany. On the other hand, chemists and biochemists—like other scientists too—distinguished themselves through precipitate obedience. In many cases the organizations acted with conformity and Jews were excluded or expunged as authors or co-editors of scientific journals without there being any corresponding legal requirement to do so.

Schleede was without doubt correct in his assumption of the international importance of German chemists. Up until the 1930s German chemists and biochemists, both in academic science and in the German chemical industry, were internationally preeminent, despite the considerable success of American and British scientists, especially in physical chemistry. After 1933, there was silence, however, about the fact

[*] Priv.-Doz. Dr. U. Deichmann
Institut für Genetik, Universität zu Köln
Weyertal 121, 50931 Cologne (Germany)
Fax: (+49) 221-4705170
E-mail: Ute.deichmann@uni-koeln.de

that Jewish chemists and biochemists had contributed extensively to this international renown since the 19th century. Thus, four of the six German Noble prize winners in chemistry up to 1918 were Jews or of Jewish descent (von Baeyer, Haber, Wallach, Willstätter), and a creative Jewish chemist, Heinrich Caro, had founded the first central research laboratory in the dyestuffs industry (BASF). Shortly after the seizure of power by the National Socialists in 1933 the participation of Jewish scientists in academic life in Germany came to an enforced end, which was followed by their exclusion from private companies and a general loss of rights. Their contribution to science was mentioned less and less.^[3]

The following contribution investigates with the keywords “flee”, “collaborate”, and “forget” the effects of National Socialism on chemistry and biochemistry in the German (and Austrian) universities and Kaiser Wilhelm Institutes (KWIs). At the center are the dismissal and forced emigration of all Jewish chemists and biochemists (from here forward (bio)chemists) and the few non-Jewish colleagues who let themselves be known as critics of the regime or as “friends of Jews”; the various forms of collaboration of scientists who did not emigrate as well as the few cases of nonconformism; and the general silence on this subject after 1945 or the attempt to allow the 12 years of National Socialist rule and their joint responsibility to slide into oblivion. The contribution is based essentially on an in-depth study of chemists and biochemists during the National Socialist era by the author.^[4] These three aspects will be discussed essentially in regard to chemists and biochemists with habilitations in Germany and Austria at that time—those who were driven from their positions and those who remained—including their research, as well as developments during the postwar years.

1. “Flee”—Dismissal and Emigration of (Bio)chemists

1.1. Dismissals and Emigrations

The comparatively large number of Jewish chemists and biochemists in German universities and KWIs, which amongst other things was associated with the professional perspectives of academic chemists in the dyestuffs industry, resulted in these specialties being greatly affected by the dismissal of all

Jewish scientists and a few non-Jewish scientists who were critics of the regime in the years between 1933 and 1938: 26 % of the chemists and biochemists (physiological chemists; most with habilitation) at the German and Austrian universities and relevant KWIs were driven from their positions; at least 20 % of all (bio)chemists emigrated.^[5] According to the then current rhetoric, about 90 % of the dismissed/emigrated (bio)chemists were forced to relinquish their positions for reasons of race, that is, they were either Jewish or non-Jews who had Jewish ancestry or were married to a Jew. The Professor of Inorganic Chemistry Hans von Wartenberg was even dismissed because his wife was “half Jewish”.

The relatively new interdisciplinary areas of physical chemistry and biochemistry, where about a third of the scientists lost their positions, were particularly affected by the dismissals (in organic and inorganic chemistry the number was about 23 %). Physical chemistry was at that time comparatively less-well regarded; the physical chemistry departments of universities were less well equipped than those of organic chemistry, and because of their relative marginalization they offered a talented minority such as the Jews the chance of advancement. Medical biochemistry was (as physiological chemistry) also one of the disciplines within the medical faculties most strongly relegated to the margins, even in the 1920s. At the beginning of the 1930s there were only a few professorships, and only in 1932 was the subject recognized as an examination subject. Biochemists were also employed at various KWIs, or as part of other university institutes of medicine, for example, pathology.

A few of the Jewish or “non-Aryan” scientists were also regarded as politically unacceptable and were in part dismissed for this reason, before they were dismissed—at the latest by 1935—as Jews. These included Professors Walter Fuchs (Technische Hochschule (TH) Aachen) and David Holde (TH Berlin), members of the Social Democratic Party, and Professor Isidor Traube (TH Berlin), who at the end of the 1920s openly supported the left-wing Heidelberg professor Emil Julius Gumbel. Wilhelm Prandtl, professor at the University in Munich, was known as a Christian (catholic) man who never returned the “German greeting”. When an invitation to visit a Party function was handed to him, he stated that he had nothing to do with the Party.^[6] In 1937 he was dismissed, not for his political leanings, however, but because his wife was Jewish.



*Ute Deichmann was born in Düsseldorf and studied biology at the Universities of Bochum and Heidelberg. For 14 years she has been employed as historian of science at the Institute for Genetics at the University of Cologne; there she completed her PhD in 1991 for her work “The Development of Biology in National Socialist Germany” and habilitated in 2000. She is also a regular guest lecturer at the Ben-Gurion University of the Negev in Israel. She is the author of *Biologen unter Hitler* (1992, 1995), that was translated as *Biologists under Hitler* (1996), and *of Flüchten, Mitmachen, Vergessen. Chemie und Biologie in der NS-Zeit* (2001), as well as of numerous reviews on the history of biology and chemistry in the twentieth century.*

In total, six people were dismissed for solely political reasons. Three of them are detailed—the others were Alfons Klemec (professor of the University of Vienna, reinstated in 1942), Ernst Terres (honorary professor at TH Berlin), and Robert Wizinger-Aust (extraordinary professor at the University of Bonn).

- 1) Otto Kraymer (Figure 1,^[*] extraordinary professor of pharmacology at Berlin, was the only scientist who refused to accept the position of a dismissed Jewish colleague (Prof. Philipp Ellinger of Düsseldorf) he was offered on moral grounds. In a letter to the Erziehungsminister (Minister for Education) he pointed out the reasons for



Figure 1. Otto Kraymer.

his decision and denounced the dismissals as unjust.^[7] He lost his former position in Berlin and he emigrated to London at the end of 1933. Kraymer's conduct in England left a deep impression: the pharmacologist Sir Henry Dale called him "*the only German gentleman*."^[8] In 1937 Kraymer accepted the position of professor and director of the Pharmacology Institute at the Harvard Medical School, where he remained active until his death in 1982.

[*] All the photos of people shown in this article were obtained from the book *Flüchten, Mitmachen, Vergessen. Chemiker und Biochemiker in der NS-Zeit*.^[4]

- 2) The organic chemist Karl Fries, professor and from 1913 head of the Chemical Institute of the TH Braunschweig, was compulsorily retired in 1938 at the age of 63 because he opposed the habilitation of a chemist whom he considered professionally unsuitable but who was a "*passionate and locally important National Socialist*."^[9] Fries then joined the institute of Professor Meerwein at Marburg where he continued with experimental research in a small space.^[10] His successor in Braunschweig was the SS member Hermann Friese.
- 3) Wolf-Johannes Müller, Professor for Physical Chemistry at the TH Wien was dismissed in 1938 because he was considered a "friend of Jews". However, he was successful in returning to his old position after about a year.

1.2. Successful Emigrants: The Effects of Emigration on (Bio)chemistry in Germany

It is not possible to name all the important (bio)chemists who were dismissed and who emigrated within this review. Instead the 25 scientifically most influential are listed in Table 1. The Nobel Prize and the number of citations in the Science Citation Index of 1945–1954 were chosen as the criteria.^[11] With the exception of Werner Kuhn, a Swiss citizen, all the people listed are Jews or of Jewish descent.

Physical chemistry in Germany was greatly affected by the expulsion, even though a few leading scientists, such as Max Bodenstein, Karl-Friedrich Bonhoeffer, Arnold Eucken, Max Volmer, and Carl Wagner, were not Jews and kept their positions. One of the physical chemistry centers was lost with the emigration of Haber and the total restructuring of the personnel in his institute—the colloquia in Haber's KWI had

Table 1. The 25 emigrated German and Austrian (bio-)chemists who received the most citations in the Science Citation Index 1945–54 (apart from recognizable own citations) and/or a Nobel Prize.

Name	Specialty	No. of citations	Nobel prize
Max Bergmann	organic chemistry/biochemistry	1880	
Hermann K. Blaschko	biochemistry	654	
Konrad Bloch	organic chemistry/biochemistry	1169	1964
Ernst Boris Chain	organic chemistry/biochemistry	588	1945
Erwin Chargaff	organic chemistry/biochemistry	1424	
Felix Haurowitz	biochemistry	671	
Hans Krebs	biochemistry	2529	1953
Fritz Lipmann	biochemistry/chemistry	1783	1953
Otto Loewi	pharmacology/biochemistry	513	1936
Otto Meyerhof	biochemistry	1467	1923
Leonor Michaelis	biochemistry	1703	
David Nachmansohn	biochemistry	1492	
Carl Neuberg	organic chemistry/biochemistry	1221	
Max Perutz	organic chemistry/biochemistry	352	1962
Rudolf Schönheimer	biochemistry	1508	
Richard Willstätter	organic chemistry/biochemistry	1556	1915
Fritz Arndt	organic chemistry	629	
Ernst D. Bergmann	organic chemistry	688	
Rudolf Lemberg	organic chemistry	645	
Fritz Haber	physical chemistry	419	1919
Georg von Hevesy	physical chemistry	1383	1943
Werner Kuhn	physical chemistry	1449	
Hermann F. Mark	physical chemistry	661	
Otto Stern	physical chemistry	98	1943
Joseph J. Weiss	physical chemistry	742	



Figure 2. Georg von Hevesy.

formed a site of interdisciplinary interaction of international repute. Georg von Hevesy (Figure 2), then one of the most important physical chemists in Germany, had begun to use radioactive tracers as markers in biology and medicine in Freiburg. He was awarded the Nobel Prize in 1943 for the development of this area of research. With von Hevesy, who in 1935 emigrated first to Denmark and then to Sweden, Germany lost an innovative, mul-

tifaceted physical chemist and a personality who had cultivated a series of contacts with leading international scientists.

The expulsion of Hermann Mark and many of his co-workers was a great loss to polymer chemistry. Unlike the founder of this research area, Hermann Staudinger (who regarded polymer chemistry solely as a branch of organic chemistry), Hermann Mark developed physical chemical methods for the investigation of polymers and devised a teaching and research program in polymer chemistry (at the University of Vienna). After his dismissal and emigration in 1938, he was later successful in establishing modern polymer science as a multidisciplinary academic research area at the Brooklyn Polytechnic Institute in the USA.

The losses to biochemistry, especially in the biochemistry of intermediate metabolism, were the most far-reaching.^[12] With the death of Gustav Embden in 1933 and the emigration of Max Bergmann, Otto Meyerhof, Carl Neuberg, Carl Oppenheimer, and, as early as 1920, Leonor Michaelis, Germany lost most of its leading biochemists. The losses in biochemistry through the emigration of Ernst Chain, Erwin Chargaff, Konrad Bloch, Hans Krebs, Fritz Lipmann, and Rudolf Schönheimer (with the exception of Chargaff all Nobel Prize winners) become even more demonstrable in the next generation of scientists. Max Perutz (Figure 3), who left Austria as early as 1936 and who was awarded the Noble Prize in 1962 for the determination of the structure of hemoglobin by X-ray structure analysis, was one of the leading molecular biologists in England. Franz Knoop, Otto Warburg, who was the only "half Jew" to retain his position as director of a KWI, and, as important biochemists of the next generation, Feodor Lynen and Carl Martius remained in Germany.

Physicists who emigrated, including the non-Jewish Dutch physicist Peter Debye, who after his emigration in 1936 received the Nobel Prize for Chemistry for his contributions to the knowledge of molecular structure, are not mentioned in Table 1. The dismissal and emigration of physicists resulted in some pioneers of quantum chemistry, in particular Walter Heitler, Fritz London, and Hans Hellmann, also being driven from Germany.^[13]

A few outstanding organic chemists also emigrated. However, the losses in classical organic and inorganic chemistry remained comparatively low overall because of the small percentage of Jewish scientists working in these areas. Most leading organic chemists and natural product chemists at that time were not Jews. Thus, the most important of them,

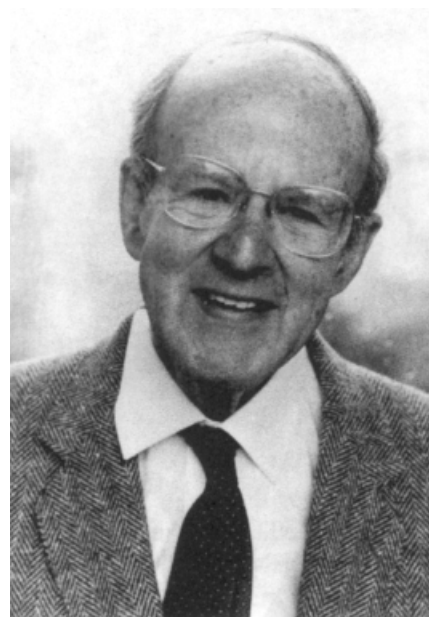


Figure 3. Max Ferdinand Perutz.

including Kurt Alder, Adolf Butenandt, Otto Diels, Hans Fischer, Richard Kuhn, Hermann Staudinger, Heinrich Wieland, Adolf Windaus, Georg Wittig, and Karl Ziegler (all of whom received Nobel Prizes in their lives), remained in Germany. Richard Willstätter had already retired when he emigrated to Switzerland. He had relinquished his position as Professor of Organic Chemistry at the University of Munich in 1924 as a protest against the several incidences of anti-Semitism in appointments at that university.^[14]

The visible deterioration in biochemistry, a few areas of physical chemistry, and quantum chemistry in Germany after 1945 is attributable to a large extent to the emigration of outstanding Jewish scientists and to the strong dominance of classical organic chemistry as well as to the rigid structures in German universities. International centers of (bio)chemistry, especially the institutes of Max Bergmann, Fritz Haber, Otto Meyerhof, and Hermann Mark, disappeared from Germany or Austria. New ones did not arise. International relations were also subject to racial stipulations: the nonscientific criteria of ancestry and political conviction were also critical for the invitation of guests.

1.3. Countries of Emigration

More than 60% of emigrants went to the countries of Western Europe, especially to Great Britain, which accepted about a third of them. In Britain, the relief organization the Academic Assistance Council, later renamed as the Society for the Protection of Science and Learning, founded by British scientists, negotiated the getting of work permits, and assisted with further emigration to the USA. At the end of the 1930s, with the start of the Second World War and the subsequent German occupation of part of Europe, many emigrants had to flee once more, and in the 1940s the large majority of the emigrants lived in the USA, followed by Great Britain, and a few non-European countries such as Turkey, Palestine, and

the countries of South America. About half of them obtained positions at universities, a fifth in industry. Older emigrants, in particular, often suffered material difficulties.

The acceptance of Jewish emigrants depended upon their reputation and specialty. In the USA, biochemistry created a niche for the outstanding scientists from Germany and Austria. With the exception of Max Bergmann, however, emigrants specializing in organic chemistry found no place at American universities; the specialty was already too far advanced to be generally interested in emigrants from Germany or Austria. To the best of my knowledge, the impact of antisemitism on American Chemistry has not yet been studied. In Palestine/Israel young chemists, especially Ernst David Bergmann (formerly of Berlin) and Ladislaus Farkas (formerly at KWI for Physical Chemistry), became exceptionally influential. This situation arose because the Zionist leader and chemist Chaim Weizmann had been successful in obtaining the necessary financing to found a new research institute, the later Weizmann Institute of Science, and because he could not entice the then best-known German–Jewish scientists, for example, Albert Einstein, James Franck, Fritz Haber, Otto Stern, and Richard Willstätter, to emigrate to Palestine. Other countries on the periphery of science also established scientific disciplines and institutions with the help of German–Jewish emigrants. Thus Fritz Arndt (formerly of Breslau) founded organic chemistry and Felix Hauowitz (formerly of Prague) biochemistry at Istanbul University.^[15] Alexander Schönberg (Figure 4) contributed decisively to the



Figure 4. Alexander Schönberg.

development of modern chemical research, particularly in preparative organic photochemistry and chemistry teaching in Egypt. German emigrants also became highly influential in Brazil, where, for example, Hans Stammreich (formerly at Berlin) at the University of Sao Paulo became a pioneer in the Raman spectroscopic analysis of colored substances.^[16] In Portugal, Kurt Jacobsohn, a former student of Carl Neuberg at the KWI for Biochemistry), founded a school of biochemical research at the Instituto Bento da Rocha Cabral in Lisbon and contributed greatly to the development of biochemistry as an independent discipline in Portugal.^[17]

Schönberg's experience in Egypt demonstrates that, in other parts of the world too, emigrants occasionally encountered problems from Germany through claims of the "Aryan master race". In 1937 Schönberg, professor at the TH Berlin

until his dismissal in 1934, became Professor of Organic Chemistry at Cairo University and Director of the Chemical Institute. Mark von Stackelberg, Professor of Physical Chemistry at Bonn University, member of the NSDAP and SA, applied for a professorship at Cairo University in 1938. When he received the prospectus from Cairo University and discovered from it that the head of the Chemical Institute (Schönberg) came from Berlin, he became suspicious. He asked the Reichserziehungsministerium (State Ministry for Education) whether Schönberg was a Jewish emigrant and asked the German legation in Cairo for information whether the dean, "in view of the fact that Arabs and Jews are at loggerheads in Palestine, would be appreciative if I were to request not to be subordinate to a Jew but at least coordinate?"^[18] In response, the Reichserziehungsministerium made it clear in a letter to the Auswärtige Amt (Foreign Office) that Schönberg had two, possibly three, Jewish grandparents and decided: "a subordination of Prof. Dr. von Stackelberg to Prof. Dr. Schönberg is totally out of the question. Prof. von Stackelberg must at least be assured the same rank as Schönberg."^[19] Those responsible in Egypt were clearly not convinced by the suggestions from Germany. von Stackelberg remained as professor in Bonn. In a judgment of the Denazification Board for Appeal of 1949 it was said of him:

"During a personal hearing, the person in question was able to convince that he had joined National Socialism originally out of enthusiasm and conviction. He had, however, not approved of everything without criticism. ... The Board has of the person in question the impression of a sincere character who has always tried to make his convictions and his conscience the guiding principle of his affairs. He cannot be blamed for the political mistake. The person in question can be regarded as fully cleared."^[20]

Schönberg returned to Berlin in 1957 on reaching the retirement age limit in Cairo. He was forced to lay claim to the status of professor emeritus at his old academy, now the Technical University of Berlin, through a legal restitution process.^[21] As his student and co-worker Erich Singer observed, he spoke extremely rarely of his past. Only when during his last months of life "the force of his self-discipline subsided through illness" did it emerge "how much he had really been affected by the flight from his mother country made necessary by the pressure of circumstance".^[22]

1.4. The Fate of Some of the Persecuted

Successful scientists who made a career in the USA or England or obtained positions in other countries constituted only a part of the dismissed and emigrated (bio)chemists. At the other end of the spectrum are those who remained in Germany or Austria without position and who suffered under increasing anti-Semitism, and above all those who either in Germany or after their flight overseas, were murdered by the National Socialists or committed suicide. These include Hans Liebermann (TH Berlin), Wilhelm Traube (Berlin University), Carl Oppenheimer (Landwirtschaftliche Hochschule

Berlin), Peter Rona (Berlin University), and Reginald Herzog (KWI for Fiber Chemistry). Also mentioned is Arnold Berliner, the founder and former editor-in-chief of the most important German and, into the 1930s, one of the leading international scientific journals *Die Naturwissenschaften*. He committed suicide when he was ordered to leave his apartment during the deportations in Berlin in June 1942.

As already mentioned, many Jewish chemists were active in the chemical industry since the 19th century. As a rule, dismissals in industry were carried out a few years later than in the universities (about 1937). As a result, many of those affected were no longer able to flee Germany in time. It is known that a few were deported and murdered in the concentration camps. These included Arthur von Weinberg (Cassella Farben; I.G. Farben supervisory board), Max Weiler (I.G. Farben, Elberfeld), Edgar Zwergel (I.G. Farben Agency, Amsterdam), Benno Strauss (Friedrich Krupp, Essen).^[23] A comprehensive investigation of the fate of Jewish industrial chemists after 1933 is currently not available.

2. “Collaboration”—Behavior of Non-Jewish (Bio)chemists 1933–1945

Every state or every political system demands of its citizens compliance with the respective laws. The height of the price of compliance with the laws of the National Socialist State can be recognized in the known abhorrent developments. With the exception of two members of the communist resistance (Robert Havemann and Georg Groscurth), none of the non-Jewish (bio)chemists in Germany were arrested for oppositional behavior. This fact cannot be explained without large compromises being made and raises the question of co-responsibility. Many conformed for opportunistic reasons without becoming convinced National Socialists. Only a few stood out through nonconformism and aid for their Jewish colleagues. A number of (bio)chemists actively supported National Socialist race ideology and policies. Collaboration was usually rewarded with generous research sponsorship by the Deutsche Forschungsgemeinschaft (DFG; German Council for the Advancement of Scientific Research) and the Reichsforschungsrat (State Research Council); political activity was often beneficial for the career.

Collaboration was carried out at many different levels, often not as a result of political pressure but precipitate obedience. It could comprise of compliance with the law on the dismissal of Jewish coworkers, silence in the face of injustice that began with the dismissals and crimes, in denunciations, in the severance of contacts with Jewish colleagues, students, and teachers, in the admission to National Socialist organizations (whether from opportunism or conviction), in political activity, in war-related research, in taking over functions in the Reichsforschungsrat, and cultural–political propaganda for foreign countries. Collaboration led finally to the enslavement and murder of internees of the Auschwitz concentration camp in the I.G. Farben facility Auschwitz–Monowitz. In the following section a few examples of nonconformity and different forms of collaboration are presented.

2.1. Nonconformity

Nonconformity and aid for Jewish colleagues and coworkers were found from a few (bio)chemists who themselves were affected by the anti-Jewish measures. The most well known example is that of Fritz Haber, who as a German state employee told his Jewish co-workers of the impending dismissal and informed the general management board of the Kaiser Wilhelm Gesellschaft (KWG) of their names, but then immediately resigned his position as Director of the KWI for Physical Chemistry in protest.^[24] Amongst the few unaffected (bio)chemists who disapproved of the National Socialists and in part helped imperiled people, often with considerable personal involvement, were the Nobel Prize winners Adolf Windaus and Heinrich Wieland as well as Max Volmer and Fritz Strassmann.^[25] Professors Max Bodenstein, Hans Fischer, and Hans Meerwein also offered assistance to some Jewish or “half-Jewish” students. “Half-Jewish” coworkers were employed during the war by Karl-Friedrich Bonhoeffer, Karl Freudenberg, Hermann Staudinger, and by the NSDAP members Rudolf Hüttel, Egon Wiberg, and Otto Westphal; this was legal until 1942.^[26]

The attitude of the head of the Institute for Organic Chemistry in Göttingen, Adolf Windaus, is described here in more detail as an example of nonconformity. He was a professor of the old school, but also a democrat and guided by a profound moralistic conscience. Unlike many of his colleagues, he had refused to become involved in research on poison gas during the First World War. Windaus did not cave in when in 1933 a group of National Socialist undergraduate and post-graduate students wanted to drive out the only Jewish postgraduate student of the Institute, Klauss Neisser, and denounced other students and co-workers at the Institute to the SA as friends of Jews. In November 1935 he wrote to the Reichserziehungsministerium that under other political conditions he would have acted energetically against the agitation in the Institute:^[27] *“I doubt, however, that I would act within the view of the Ministry, and it is not my intention to oppose my superior authorities.”* He saw in resignation the only way out, for: *“I am too old to be able to change the ethical perspectives with which I have grown up.”*

In contrast with Haber, who in 1933 requested his retirement for a similar reason, the Ministry was conciliatory towards Windaus when it met his conditions: the leading activists had to change university. Windaus (Figure 5), who never greeted with the Hitler salute or signed with “Heil Hitler” and openly professed that he disliked the then political developments, was persuaded to remain in office. In this case, the continuance of the world-renowned research of the Nobel Prize winner Windaus was more important to the science politicians than the fulfillment of the political–ideological demands of the stu-



Figure 5. Adolf Windaus.

dents. After obtaining his doctorate in 1935 Klaus Neisser emigrated to Brazil.

Windaus found—and was here, too, an exception—the anti-Jewish movement at the beginning of 1933 an almost intolerable injustice that had devastating effects on chemistry in Germany. Thus, on the 10th April, 1933 he wrote to his former student Adolf Butenandt:^[28]

“Unfortunately I am lacking that feeling of inner peace to enjoy my every day. To have to look at injustice and not to be able to help is difficult to bear. I have just come from Kaiserstrasse. A man was standing there shouting: ‘the Jews are being destroyed’. Even if he did not mean bodily destruction it annoyed me that the police left him alone to agitate. It is distressing to see how pernicious instincts are so easily awakened, brutality, hatred, jealousy, and how quickly all feeling for justice and humanity is lost.”

“That Schönheimer’s going is a great loss. What do these men know that Haber ensured nitrogen supply during the war and that he had organized the whole gas campaign! What do they know how highly Willstätter is regarded in other countries and what he has achieved for German science and through it for the economy. At this moment people are carrying past placards on which stands the most unbelievable and hellish slander against the Jews.”

Windaus was the only university teacher of chemistry who sought a dispensation for participation in the Haber commemoration in January 1935 (he was refused). University teachers would have been able to take part legally with such a dispensation from the prohibition on participation issued by the Reichserziehungsminister Rust. The board of the Deutsche Chemische Gesellschaft refused participation from the start, and the Verein deutscher Chemiker (Association of German Chemists) forbade participation in the commemoration in a written communication to its members (see below).

As the above citation shows, Windaus was a German state employee who essentially discharged his duty of obedience to the State. In 1935 he turned down an offer from the University of Chicago. The reasons for this are unclear, but it is possible that his age played a role—he was 59 years old in 1935. Windaus, however, stood out through his unusual moralistic integrity, an integrity which was also revealed in his research in which he repudiated speculation and admitted to errors.

The (bio)chemists Robert Havemann and Georg Groscurth belonged to the communist resistance.^[29] The resistance group “European Union”, founded by them in 1942, was denounced in 1943, and many of its members, including Havemann and Groscurth, were sentenced to death. Whereas Groscurth was executed on the 8th May, 1944, Havemann received a deferment of execution and he survived thanks to a number of professors of chemistry and pharmacology who succeeded in convincing the authorities that his research was vital for the war effort.^[30]

In 1935 a number of chemists in industry did not behave with conformity. They protested, however, not against the National Socialist regime but against the board of the Verein deutscher Chemiker. Its ban issued against participation in the Fritz Haber commemoration resulted in a large number of letters of protest and even resignations.^[31] Members of the

association, including also those who made no secret of their anti-Semitism, protested not only because they felt unjustly censured, but because they did not agree that a commemoration for this outstanding German scholar and patriot should be forbidden. There are no indications that the protest resulted in professional disadvantages. Chemists at universities and KWIs did not protest.

2.2. Acceptance of the Anti-Jewish Measures

It is one of the most notable phenomena in academia in 1933 that the severest measures of National Socialist policies against science were carried out under a high degree of silence and with the frequent consensus of scientists: the persecution of Jews and people with Jewish ancestry, who often identified themselves with the German nation and culture, took place without public reaction on the part of the non-Jewish colleagues and, in most cases, even without private protest or signs of compassion.^[32]

The reaction of the noted Heidelberg organic chemist Karl Freudenberg to the criticism of the dismissals by his colleague George Barger at Edinburgh University highlighted an attitude that was widespread in Germany. In his letter to Barger, Freudenberg (Figure 6), who maintained personal relationships with Jewish colleagues (including Max Bergmann and Hermann Mark) and who did not become a member of the NSADP, welcomed the dismissal of his Jewish colleagues as a necessary remedy for German ills: *“It is a matter of orders with which one has simply to conform. I am fully convinced that a cure at the heart of the German nation was necessary, and is disputed by but just a few. As to the method by which it was carried out, no lengthy reflections can be engaged upon in this country since it is a matter of command and it is entirely immaterial where the individual stands on this.”*^[33] The fact that Hitler was a putschist and used terror as well as political violence to ensure power also represented no

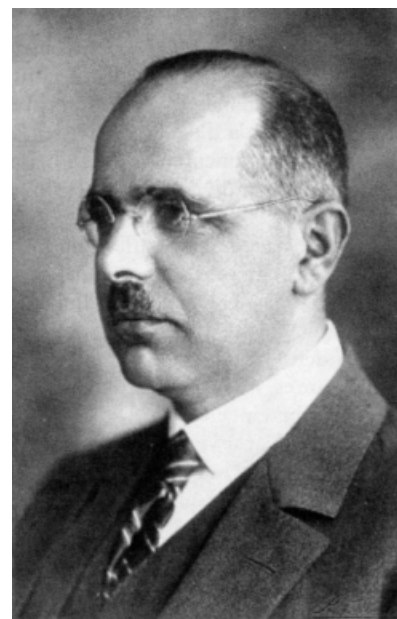


Figure 6. Karl Johann Freudenberg.

hindrance within academic circles to their unconditional support. Thus according to Freudenberg, “amongst most educated Germans the recognition for that achieved is prevalent (...). We have a unified central government of considerable power, and at the head of it an absolutely fine man who simplifies the administration with considerable energy.”^[34]

Freudenberg's letter enables anti-Semitism and the tradition of obedience of German civil servants, which include university teachers, to be recognized as two motives for the silence and the agreement to the dismissals. The historian Saul Friedlander differentiates between the “cultured Judeophobia”, which characterizes the attitude of the majority of “Aryan” professors, and the radical form of Judeophobia which developed amongst students.^[35] A further motive—taking advantage—played a role mainly with younger academics and students who obtained the positions of those dismissed. These various motives had the result that non-Jewish scientists who otherwise differed clearly in their attitude and behavior towards the National Socialist regime almost without exception accepted the dismissals without comment and to a certain extent with approval. Examples are the openly National Socialist and anti-Semite Wolfgang Ostwald, the compliant but nonmembers of the NSDAP Karl Freudenberg and Paul Harteck (physical chemist, former assistant of Haber), Karl-Friedrich Bonhoeffer, who otherwise rejected National Socialism, and the communist resistance member Robert Havemann.^[36] Unlike in physics, the anti-Semitism amongst chemists was not associated with the rejection of certain research fields as “Jewish”, but was directed mainly at the exclusion of Jewish colleagues amongst scientists and students.

As civil servants, German professors had a duty of obedience towards the State. However, unlike their younger colleagues without tenure, they would have been able to voice a certain amount of criticism without endangering their position. The large majority of professors and directors, however, followed the regulations on the dismissal of Jewish co-workers to the letter, and many, such as Arthur Schleede cited at the beginning, took the initiative themselves when it came to the exclusion of Jews from scientific life in Germany.

Precipitate obedience also defined the behavior of Richard Kuhn, the head of the Institute for Chemistry at the KWI for Medical Research (Figure 7). In 1933 he dismissed his Jewish co-workers without the least effort to keep them longer, and in 1936 he denounced his colleague Otto Meyerhof to the General Council of the Kaiser Wilhelm Gesellschaft because he continued to employ Jewish co-workers. Kuhn, one of the most important natural product chemists in Germany, did not want to run the risk of the slightest disadvantage or bad reputation for the Institute; there is no indication that he was an anti-Semite. In 1939 Kuhn was awarded the Nobel Price for Chemistry for 1938, but



Figure 7. Richard Kuhn.

refused the honor, as did Gerhard Domagk and Adolf Butenandt, because after January 1937 the National Socialist government in Germany no longer allowed the acceptance of the Nobel Prize. Under political pressure, Kuhn (as did Butenandt and Domagk) wrote a sharply worded letter to the Royal Swedish Academy of Science in which he not only refused to accept the prize but labeled the award of the prize to a German as an attempt to provoke the prize winner into contravention of a decree of the Führer.^[37] Kuhn wrote by hand at the bottom of the letter: “*The Führer's will is our belief*.”^[38]

The inorganic chemist Wilhelm Klemm also resorted to denunciation to prevent contributions from Jewish or “non-Aryan” authors appearing in future German chemical journals. In June 1942 he sent the editorial staff of “Berichte” an official letter on the “non-Aryan” descent of Georg-Maria Schwab, and on the strength of it the managing editor, A. Ellmer, abandoned the publication of a new contribution from Schwab.^[39] I am not aware of Klemm's motive; he had been professor in Danzig since 1933, in 1938 he became a member of the NSDAP, and in 1951 professor in Münster. During the National Socialist era the editors of purely scientific journals were not forced to undertake research into the Jewish descent of authors. Thus, at least up to the denunciation by Klemm, contributions from Schwab appeared in a number of German journals (apart from “Berichte”, the *Zeitschrift für Physikalische Chemie*, the *Kolloid-Zeitschrift*, and the *Viennese Chemiker Zeitung*). Schwab, himself a catholic, had a Jewish father and was therefore dismissed and he emigrated to Greece.

The difference between the essentially voiceless adherence to the dismissal of Jewish colleagues and co-workers and the criticism of other political science measures, for example, the increasing centralization of education and the deprivation of the power of faculties in matters of appointment, is remarkable. Other regulations were also sometimes avoided, thus, for example, after 1940 a number of chemists continued with their fundamental research under the label “research important for the war effort”.

Anti-Semitism also occurred in the chemical industry. One example is the long-standing board member of I.G. Farben, Heinrich Hörlein, who joined the NSDAP in 1933. On his instigation, the Deutsche Chemische Gesellschaft had already urged its Jewish president (Alfred Wohl) and vice president (Artur Rosenheim) to resign in May 1933. In April 1933 Dr. Hermann Kretschmar, leader of the chemistry group in the Kampfbund für deutsche Kultur (Front for German Culture) and member of the Deutsche Chemische Gesellschaft wrote that he knew that Hörlein “as only member of the board [of the Deutsche Chemische Gesellschaft] had put a stop to Jewish infiltration”.^[40] Hörlein became director of Bayer-Werke after the war.

2.3. Political Good Behavior and NSDAP Membership

Political adaptation, whether it be from conviction, opportunism, or both, also manifested itself amongst (bio)chemists (as in other academic disciplines) in the joining of National

Socialist organizations. About 53 % of the (nondismissed) academic (bio)chemists became members of the NSDAP (in the case of biologists 57.6 %) and 7.2 % members of the SS (in the case of biologists 5.3 %).^[41] A larger percentage of younger scientists joined the NSDAP: of those under 40 years of age, it was about 63 %. Of a total of 93 (bio)chemists appointed professors between 1933 and 1945, 59 (63 %) were members of the NSDAP. 28 (bio)chemists, 11 of them physical chemists, had already joined the Party prior to 1933. It may be assumed that this group, at least, consisted of committed National Socialists. Eleven of them became professors at the latest by 1945, including four who were also members of the SS.

Membership of National Socialist organizations was not mandatory for habilitation and professorship, but it often facilitated it. Principally, younger scientists at smaller universities were to some extent under considerable pressure to join one of these organizations. Party membership therefore did not necessarily mean National Socialist conviction (a number of nonparty members also supported national socialist politics in other ways). It must also be mentioned that a few of the younger scientists did not yield to pressure and were therefore ready to suffer the consequences. Amongst those who were, in spite of this, appointed professors were the organic chemist and later Nobel Prize winners Kurt Alder (1940 in Cologne) and Karl Ziegler (1938 in Halle), the biochemists Hans Hermann Weber (1939 in Königsberg) and Karl Lohmann (1937 in Berlin), and the physical chemists Klaus Clusius (1936 in Munich), Wilhelm Jost (1943 in Leipzig), and Carl Wagner (1939 in Darmstadt). In the case of Jost, at least, the fact that he was not a member of a National Socialist organization delayed his appointment for a number of years.

The colloid chemist Wolfgang Ostwald, an NSDAP member from 1933, is an example of how a mere average scientist attempted—with partial success—to improve his academic position through party political engagement and collaboration. His engagement took the form of National Socialist propaganda in the USA and England as well as in Eastern European countries where he made special efforts to awake understanding for the anti-Jewish measures in Germany. He used the remarkable metaphor “recrystallization” for this, as he wrote in his report on his journey: “*as chemists they understood me best if I spoke of our revival as of a ‘recrystallization’, that is purification, stabilization, reforming, etc.*”.^[42]

A few scientifically notable (bio)chemists also joined National Socialist organizations, as the examples of Adolf Butenandt and Hermann Druckrey demonstrate. Butenandt (Figure 8), successor to the dismissed Carl Neuberg as Director of the KWI for Biochemistry, became a NSDAP member in 1936. In 1939 he was awarded the Nobel Prize for his pioneering research on steroidal hormones, which, as mentioned in Section 2.2, he had to refuse. His co-worker Günther Hillmann advised the head of the neighboring KWI for Anthropology, Otmar von Verschuer, how blood from artificially infected concentration camp inmates sent by Mengele from Auschwitz was to be investigated biochemically. The conclusion may be drawn from this fact that



Figure 8. Adolf Butenandt.

Butenandt was aware of the collaboration of his colleague von Verschuer with Mengele in Auschwitz.^[43] He disputed this after the war and moreover contributed to the defense of von Verschuer with a testimonial authored in cooperation with Max Hartmann, Wolfgang Heubner, and Boris Rajewsky. Butenandt remained Director of the KWI (now the Max Planck Institute) for Biochemistry and became President of the Max Planck Gesellschaft in 1960.

The long-standing National Socialist Hermann Druckrey (member of the NSDAP from 1931 and the SA, where in 1943 he rose to Oberführer) was an internationally renowned cancer researcher. Presumably, because of his political activity, Druckrey never did receive a professorship after the war, but in 1948 he became head of a laboratory at the Surgical University Hospital in Freiburg, which became the Research Unit for Preventative Medicine of the Deutsche Forschungsgemeinschaft (DFG) after 1952. In 1956 the DFG elected him to chairman of the Dyestuffs Commission. In 1954 Druckrey became chairman of the Cancer Prevention Commission in New York, in 1956 member of the WHO Advisory Panel in Geneva on Food Additives, and member of the Italian Society for Cancer Research in Milan and the Royal Society, Medicine Section, in London.

The rapid political adaptation in chemistry is clearly demonstrated by the example of the Verein deutscher Chemiker, the “*only recognized professionally representative body of German chemists*” to which both university teachers and students as well as industrial chemists belonged. Under its chairman Paul Duden, member of the board of directors at Hoechst, the Association implemented conformity (Gleichschaltung) at a members’ meeting as early as June 1933 by excluding Jewish members and introducing the Führer principle; Duden was appointed “Führer” of the Association by the Association’s Board.^[44] In 1934 the Association joined the Reichsgemeinschaft der technisch-wissenschaftlichen Arbeit (State Society for Technical and Scientific Endeavor), an association of a number of National Socialist led societies under Dr. Ing. Fritz Todt.^[45] Todt was then head of the Hauptamt für Technik (Central Office for Technology) of the NSDAP and he became Reichsminister für Bewaffnung und Munition (State Minister for Armaments and Ammunition)

in 1940. In the new articles of the Association the promotion of chemistry “by scientific and technical encouragement and support and the inculcation of its members into the National Socialist community” was given as the objective of the Society.^[46]

The Deutsche Chemische Gesellschaft did not officially implement conformity in 1933, but in precipitate obedience it replaced Alfred Wohl, a Jew elected president in 1932, by the inorganic chemist Karl Andreas Hofmann after just one year in office. In 1938 Richard Kuhn became president of the Society, an office he held until 1945. He submitted to political pressure from the Hauptamt für Technik of the NSDAP and agreed to the linking of the Society to the National Socialist Bund Deutscher Technik (Union of German Technology) and thus to its implementation of conformity.

2.4. Research and Politics

(Bio)chemists who had proved their non-Jewish descent and did not openly criticize the regime enjoyed wide-ranging freedom in the choice of research topics and, apart from war-related constraints, material support. Thus, when questioned by representatives of the Rockefeller Foundation after the end of the war, Adolf Butenandt emphasized the freedom which he had enjoyed as a scientist from the First World War up until the end of the National Socialist era, and had only been seriously hindered by the occupation policies of the Allies.^[47] The research support of (bio)chemists by the Deutsche Forschungsgemeinschaft and the Reichsforschungsrat increased by a factor of 13 from 1933 to 1944—the increase was considerably greater than that of the support of academic research by industry—and a further source of finance was the Wirtschaftministerium (Ministry for Economic Affairs) with the newly founded Reichsamt für Wirtschaftsausbau (State Office for Economic Development) which financed mainly applied research.^[48] Both important scientists, such as the then or future Nobel Prize winners Adolf Butenandt, Hans Fischer, Richard Kuhn, Hermann Staudinger, and Karl Ziegler, and totally insignificant researchers, including those whose careers were mainly politically motivated, were supported by large sums of money.

Examples of successful research are the natural product work of Butenandt and Kuhn, Druckrey's investigation of chemical carcinogens, the further extension of their diene synthesis by Kurt Alder and Otto Diels in 1928, and the discovery of nuclear fission by Otto Hahn, Lise Meitner, and Fritz Strassmann.

On the other hand, under the conditions of National Socialism, where the power of persons in leading positions was strengthened, criticism of power was more suspect than previously, and with increasing international isolation, criticism from abroad was no longer taken seriously (especially when it came from Jewish scientists) and poor science and fake results were able to exert greater influence than before (naturally, not all cases of fraud at this time are attributable to National Socialism). The research of the Halle professor and president of the Akademie der Naturforscher Leopoldina, Emil Abderhalden, on defense enzymes, which were later

proven to be nonexistent, is an example. This research, the results of which could not be reproduced by Leonor Michaelis in Germany or by American researchers as early as 1914–1916, was extended and propagated by Abderhalden (Figure 9) as a basis for many medical uses, such as cancer diagnosis or the diagnosis of psychiatric diseases, during the National Socialist era. Abderhalden never retracted his results.^[49] Only after his death in 1950 did the concept of defense enzymes slowly disappear from textbooks.

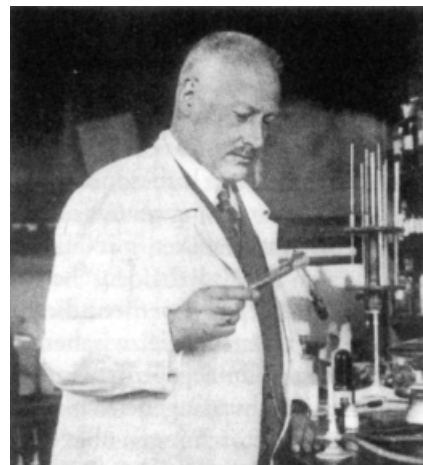


Figure 9. Emil Abderhalden.

Cancer research, especially research into the causes of cancer, was financially one of the most greatly supported areas of medicine.^[50] It included research aimed at the identification of X-rays and chemicals as carcinogens, including carcinogens at the workplace. Hermann Druckrey (see Section 2.3) successfully investigated the carcinogenic action of azo dyes and their precursors, including aniline. Butenandt's extensive project on the experimental investigation of the formation of tumors by steroids, especially steroidal hormones, and their metabolic products was also supported within this context.

Cancer research was also an area in which cases of fraud mounted. Thus, the main part of biochemical research into the early recognition and serodiagnosis of cancer was based upon the use of the method of the Abderhalden defense enzymes, and, irrespective of whether this method is regarded as self-deception or fraud, was therefore totally valueless. A number of other biochemists based their research on the sensational discovery of the German organic chemist Fritz Kögl in Utrecht, who in 1939 allegedly demonstrated that proteins in tumor tissue differed from those in normal tissue in that they showed a higher content of D-amino acids, particularly D-glutaminic acid, a discovery which was later shown to be a falsification by a co-worker. Ernst Waldschmidt-Leitz, Professor of Organic Chemistry at the German University in Prague from 1937 combined Kögl's assertion with the concept of Abderhalden defense enzymes and proposed the thesis that the D-peptidases apparently existent in tumor tissue could be regarded as a defense reaction against the tumor and could be used as therapy. He even spoke openly of the possibility of a tumor vaccine. At the initiative of the DFG

and the foreign section of the Reichsärztekammer (State Medical Association) his promises were published in a Viennese journal as a propagandistic demonstration of German research success. This is an example of the fusion of fraudulent research with propaganda in a society ideologically influenced by National Socialist propaganda.^[51]

After 1933 there was a small group of researchers who pursued the development of a “German chemistry” under racial viewpoints. The organic chemist Conrad Weygand, the physical chemist Karl-Lothar Wolf and his students Rembert Ramsauer and Helmut Harms were amongst their number. The efforts of these outsiders to a “German chemistry” encountered no appreciable interest, either from professional colleagues or political circles, and had little influence upon chemical research or teaching.^[52]

There was no appreciable ideological pressure on chemistry, as was exercised for a time in physics on the representatives of quantum mechanics by propagandists of the anti-theoretical “Aryan physics”. This can be explained on the one hand by the fact that the importance of chemistry, including academic chemistry, was clear from the start for the economic and military objectives of National Socialism, and on the other by the fact that the area of theoretical chemistry, particularly quantum chemistry, was for the reasons explained in Section 1.2 only weakly represented prior to 1933 and thereafter further weakened by emigration.

The four-year plan and the demands made of scientists after 1939 to undertake research important for the war effort led to a significant increase in work which served the aims of economic self-sufficiency or were war-related. After 1939 a large number of (bio)chemists carried out (at least officially) research important for the war effort or for the State, although labeling research a “state” or “war” priority did not in every case mean that it was not of significance for fundamental research. The most greatly supported projects of importance to the war effort included research on synthetic fuels, questions of friction and lubrication in high-performance engines, improvements to plastics, and research into materials for chemical weapons.

Chemical war gases were produced and in use against international law during the First World War. The initiative for this came from scientists themselves, notably from Fritz Haber, who cooperated with industry and the military and was supported by prominent German academics.^[52] Carl Duisberg, director general of the Farbenfabriken Bayer and later chairman of the supervisory board of I.G. Farben, played a prominent role in the industrial development of chemical war gases. During the National Socialist era too, scientists—of different ideological persuasions—cooperated with industry and the military in research on war gases. Research was carried out both on war gases such as mustard gas and phosgene, which had already been used during the First World War, as well as on the nerve gases tabun and sarin, newly discovered by the I.G. Farben chemist Gerhard Schrader as part of his research into phosphorus-containing insecticides. These materials were developed further into usable war gases by I.G. Farben.^[53]

Many chemists at KWIs and universities undertook research into war gases; two directors of KWIs, Peter Adolf

Thiessen and Richard Kuhn, undertook it with particular intensity. Thiessen (Figure 10), already an activist for the SA and NSDAP in the 1920s, identified himself explicitly with the economic–military and ideological aims of the new state.



Figure 10. Peter Adolf Thiessen (3rd from the left) with Erich Hückel, Peter Debye, Klaus Clusius, and H. H. Franck.

Thus, in 1936 he supported the propaganda exhibition “Germany” initiated by Joseph Goebbels, and Goebbels thanked him personally.^[54] On the May 1st, 1940 Hitler accepted the KWI into the ranks of the “Model National Socialist Operations” with the award of the Golden Flag.^[55]

The KWI with Thiessen as director was especially well funded.^[56] Besides the high support grants from the DFG/RFR, Thiessen received financial support from I.G. Farben, the Wirtschaftsministerium, and the army. Research was undertaken mainly into the area of application-oriented colloid chemistry and less closely defined toxic gases. A considerable part of the research effort was considered secret and was not published. The existence of a pharmaceutical–chemical section funded by the Heereswaffenamt (army ordnance office) suggested that research into the development of chemical weapons was being carried out at the Institute itself. Thiessen also installed a war-gas research section at the war-gas production facility in Falkenhagen.^[57]

In spite of the change in research to topics important for the war effort, the intensity and effectiveness of the war-gas research at this institute was significantly lower than during the First World War when the whole institute was involved in war-gas research after appropriate extension. The history of the KWI for Physical Chemistry illustrates the continuity in the cooperation of the elite from the state, military, and science under National Socialism. It illustrates the change of the old nationalism, which included Jews and allowed a scientist such as Haber to develop and use toxic gases for the nation, and the new nationalism, in which there was no place for Jews, regardless of their political persuasion. It shows, just as in the following example of Richard Kuhn, that chemists in leading positions also worked on new war gases and their antidotes during the Second World War—research which was a requirement for their possible use. War-gas research also took place in other European countries and in the USA. Here a view of the political context is important: German scientists knew that they supported the imperialistic and (in the east) genocidal war aims of Hitler with their research on these mass destruction agents.

From 1945 to 1956 Thiessen was involved in research into the separation of uranium isotopes as part of the atom bomb project in the USSR. After this period he lived in the German Democratic Republic (GDR). In 1956 he became a professor at the Humboldt University, Director of the Institut für Physikalische Chemie der Akademie der Wissenschaft in Berlin, and in 1957 chairman of the Forschungsrat (Research Advisory Board) of the GDR, in whose founding he was involved.^[57b]

Reports from allied intelligence teams and statements from previous co-workers confirm that during the war Richard Kuhn investigated nerve gases of the tabun–sarin series in the KWI for Medical Research in Heidelberg headed by him, and carried out experiments on the development of antidotes.^[58] The poison gas section of the Heereswaffenamt regularly sent Kuhn compounds of the tabun–sarin series from other laboratories so that he could test these and compounds synthesized by himself for their activity in a procedure developed at Heidelberg. Thus, Kuhn experimented with nerve gases of the tabun–sarin series in his institute. In spring 1944 he was successful in developing a new nerve gas called soman which was more toxic than sarin. Kuhn was in contact with Hitler's former personal physician, Karl Brandt, who had been appointed by Hitler as commissioner for gas protection, and in the summer of 1944 discussed with him possible methods of treatment for tabun and sarin poisoning.^[59]

According to information from Kuhn, the Heereswaffenamt terminated his research into poison gas in September 1944. All relevant documents were removed and the destruction of laboratory notebooks was ordered. During his interrogation by the allies, Kuhn stated that he had not carried out any further research in the area of soman. All the documents were allegedly buried in a mine shaft about 15 km east of Berlin, and their complete contents taken to the Karpov Institute in Moscow by Professor Colonel Kargin. The background to the order by the Heereswaffenamt to cease research into poison gases was not given. Kuhn remained director of the KWI/MPI for Medical Research in 1945, and in 1950 he was appointed a full professor at Heidelberg University and in 1955 vice-president of the Max–Planck Gesellschaft.

Kuhn was an outstanding scientist who after 1933, and especially during the Second World War, placed his scientific activities and his organizational talent at the service of National Socialist Germany. His achievements as chemist, his nationalism (which also prompted him to fundamental affirmation of the national socialist regime), his ability to maneuver between politics and science, and his opportunism explain at least in part his power during the National Socialism period. Erwin Chargaff characterized Kuhn as “*a Karajan of chemistry. Essentially he was very good, but he degenerated politically, like Heisenberg.*”^[60] Otto Meyerhof accused Kuhn “*of having freely placed his remarkable scientific ability and mastery of chemistry at the service of the regime whose unspeakable heinousness and infamy*” was “*well known*” to him.^[61] Like Heisenberg, Kuhn belonged to those scientists who, regardless of whether they were convinced of the National Socialist ideology, supported the regime with their reputation and were ready (in the case of Kuhn partially

successfully) to develop for Hitler agents of mass destruction. In this way they were not only co-responsible for the injustices of National Socialism but damaged science in Germany far beyond the era of National Socialism.

2.5. Crime

The greatest crime of chemistry was the production and use of cyklon B, a product of the Deutsche Gesellschaft für Schädlingbekämpfung (German Society for Pest Control), controlled by the I.G. Farben, for the industrial destruction of humans and the exploitation of Jewish and other slave workers in the I.G. Farben-Werk in Auschwitz. (Only brief mention can be made here to the considerable number of publications on this topic.^[62]) The Nuremberg I.G. Farben Trials of 1947–1948 made this crime known to the public at large. Twenty four leading employees of I.G. Farben, including the chairman of the supervisory board (and honorary Professor for Chemistry at Berlin University) Carl Krauch, Director General Hermann Schmitz, the I.G. Farben expert for butadiene polymerization and poison gas and head of the facility for synthetic rubber at I.G. Farben-Werk in Auschwitz Otto Ambros, and all other members of the board of directors were accused by the Nuremberg Military Tribunal. The main point of the accusations concerned slavery and mass murder. The chemists and industrialists were accused of having enslaved and killed the civilian population, prisoners of war, and concentration camp inmates. The judgment, which was pronounced on the July 29th, 1948, marked the beginning of the cold war in which West Germany became an alliance partner of the Western Allies. Thirteen of the accused received prison terms which stretched from one and a half to eight years, including the above-mentioned Otto Ambros, who like Walter Dürfeld was sentenced to eight years imprisonment, Fritz ter Meer to seven years, and Heinrich Bütefisch and Carl Krauch to six years each.

3. “Forget”

3.1. General

There was no open discussion in Germany in the sciences after the war of the anti-Jewish measures after 1933 and of the past of their coprofessionals, their support of National Socialist ideology and policies, and involvement in crime. Biologists did not involve themselves critically with, for example, the political past of the behavioral scientist Konrad Lorenz, who had openly welcomed and scientifically legitimized national socialist race policies (and was awarded the Nobel Prize in 1973).^[63] Human geneticists (anthropologists, eugenicists, and psychiatrists) refused to grapple with the ideological and practical contribution of their discipline to the National Socialist policies of selection and annihilation.^[64] Max Weinreich's book *Hitler's Professors, The Part of Scholarship in Germany's Crimes against the Jewish People*, published by YIVO in New York, 1946, in which the author drew attention to the central role of human geneticists and jurists in the

crimes of the national socialists against Jews, was never translated into German.

German physicists were unsuccessful in the construction of a nuclear reactor and an atomic bomb. Their representatives, especially Werner Heisenberg and Carl-Friedrich von Weizsäcker, spread the rumor after the war that German physicists had not produced the atom bomb for moral reasons. Robert Jungk, who from a lack of background knowledge had contributed considerably to the spread of this rumor in 1956 with his book *Heller als Tausend Sonnen*, recognized later that he had been misled. Thus in the preface to *Die Uranmaschine* by Mark Walker he wrote: “That with the translation into many languages of my 1956 book ‘Heller als Tausend Sonnen’ I had contributed to the myth of passive resistance of the important physicists is attributable to my high esteem for these personalities which I have had since to recognize as inappropriate.”^[65] This legend was finally destroyed in Germany in 1992 when the British government released tape recordings which documented discussions with German nuclear physicists interned in the British Farm Hall after the war.^[66a] In 1947 the physicist Samuel Goudsmit had already shown in the USA that this legend had been invented by a number of German physicists themselves, in particular C.-F. von Weizsäcker, in Farm Hall when they received news of the dropping of the American atomic bomb on Hiroshima. Goudsmit attributed the failure of the German uranium project under Werner Heisenberg to deficiencies in scientific organization, the errors and inability of individual scientists and their complacency. (His book was never translated into German.)

3.2. Absent Discussion of Auschwitz

How did the situation appear in chemistry? The central role of the chemical industry in the genocide at Auschwitz has certainly been mentioned in a number of individual publications, but it has never been the subject matter of open discussion to the same extent as that of the (American) atom bomb, neither immediately after the war nor at any time since.^[67] Chemists have themselves remained silent or denied the known participation of I.G. Farben representatives in the crime. The political past of many scientists or their research on poison gas was not the subject matter of open criticism.

In the years 1946 to 1950 neither Auschwitz nor the Nuremberg Trials were subject of comment in *Angewandte Chemie*, the mouthpiece of the chemical societies in the different zones of Germany after 1945 (although it was mentioned in the *Physikalische Blätter*, see the 1948 letter from the GDCh board below). The only allusion to the injustice towards Jewish colleagues during National Socialism is found in a discussion of the autobiography of Richard Willstätter^[14a] by Rudolf Pummerer.^[68] As the inventor of E 605 (1944) and other insecticides, Gerhard Schrader (see Section 2.4) was honored with the silver Ehrenplakette for services to agriculture and the Otto Appel Denkmünze in 1955. In 1956 the Gesellschaft Deutscher Chemiker (GDCh) awarded him the Adolf von Bayer Denkmünze “in recognition of his outstanding services in the discovery of novel and highly effective pesticides based upon phosphate esters...” The

portrait of Schrader published on this occasion by Burckhardt Helferich, the President of the GDCh, in *Nachrichten für Chemie und Technik* (1956, 4, 286) made no mention of his work on tabun and sarin. In a celebration held by the GDCh to mark the 80th birthday of Alwin Mittasch in 1950 it is stated without further comment: “men such as Carl Krauch, Christian Schneider, Christoph Beck, Matthias Pier are amongst the best of their profession.”^[69]

On the other hand chemists criticized the indictment of prominent members of the I.G. Farben board of directors in Nuremberg. Karl Freudenberg wrote to his colleague Paul Karrer in Switzerland: “our friend Hörlein and his companions in suffering are a cause of concern to us. Not that they have done anything wrong, but because the intention to not to allow the submission of any justification is becoming clear. This situation must be given the greatest attention. ...”^[70] Freudenberg made a significant contribution to the defense of the chairman of I.G. Farben (Carl Krauch) and Adolf Butenandt as well as to the acquittal of the director of the Elberfeld facility of I.G. Farben (Heinrich Hörlein), who had been accused of being responsible for pharmacological experiments with methylene blue on prisoners in concentration camps.^[71]

After the announcement of the judgment in the Nuremberg I.G. Farben trial, the GDCh, that is, the academic chemists, tried to lodge an appeal with the military governor and justice of the American zone, General Clay, by referring to the coercions of total war.^[72] Their letter shows that chemists did not then recognize the atrocious occurrences in the I.G. Werk Auschwitz and the responsibility of individual leading members of I.G. Farben.^[73]

“Following expressed approval of this submission by the members at attendance at the general assembly in Hanover the Council of the 4500 membered Gesellschaft Deutscher Chemiker requests you, General, to refuse the necessary confirmation of the sentence passed by the American Military Court in Nuremberg against 13 directors of the previous I.G. Farben Industry.

We know the convicted to be honorable men from work over many decades. We are of the opinion that the methods used by the prosecuting authorities are not in keeping with the methods previously stipulated in Germany prior to the Hitler regime and in the United States of America. We are further of the view that the judges did not take into account the circumstances of total war in a dictatorial state ruled by terror. We do not understand the severity of the prison sentences imposed on men who in our opinion are in this way unjustly made comparable to common criminals. We cannot believe from our knowledge of the convicted that dishonorable thought or deeds have really been proven against them. The strive for understanding between nations filling us all, is made difficult by this judgment. We would be very thankful, General, if you interceded so that the judgment is set aside by the American Federal Court, whose judges are respected throughout the world.”

It is remarkable that the peoples of nations who themselves or their relatives were enslaved or murdered in Auschwitz continue to be ignored in the strive towards international understanding. A precondition for understanding would have

been to allow them to experience justice in retrospect by punishment of those guilty. The Italian chemist Primo Levi, a Jewish slave worker in Auschwitz, has discussed this topic in many publications.^[74]

Industry joined the criticism of the Nuremberg judgment. A meeting of the “Arbeitsgemeinschaft Chemische Industrie des Vereinigten Wirtschaftsgebietes” (Chemical Industry Federation of the Unified Economic Area) in Cologne on the October 14, 1948, at which numerous senior officials of government, justice, and administration were present, was openly critical in front of the press.^[75] The main preoccupation of the chemical industry was to prevent further damage to its image. An altercation with the Nuremberg Trials was at least avoided in the chemical journals. It was not the involvement of its own kind in the crime which caused disquiet, but the publication of Willstätter’s autobiography in 1949, in which Willstätter implied anti-Semitism on the part of the founder and long-term director of I.G. Farben, Carl Duisberg.^[76]

Only in 1988 in a commemorative publication of Bayer Werke, one of the successor companies of I.G. Farben, was the murder of slave workers in the construction of a new major facility of I.G. Farben for the production of artificial rubber and synthetic fuel in Auschwitz acknowledged. There it is stated: “according to the ‘Jewish Conference on Material Claims against Germany’ a total of about 38,000 prisoners, mostly of Jewish descent, had to work at the site [major facility for I.G. Farbenindustrie in Auschwitz] from 1941 to 27th January, 1945. It is assumed that more than 30,000 of these people perished.”^[77]

3.3 The Amnesia of the Kaiser Wilhelm Gesellschaft (Max Planck Gesellschaft) and Universities

The exclusion or denial of the historical truth, which is particularly striking with the example of chemists and the crimes in Auschwitz, characterizes the whole of the German post-war history at universities and in the Kaiser Wilhelm Gesellschaft. Thus, the Tübingen university lecturer Walter Jens found during an inspection of documents of Tübingen University that “the protocols from the era after 1945 [were] most eerie: as if nothing had happened! No Stalingrad, no Auschwitz, no eugenic sterilization, and no scientific ennobling of anti-Semitism! ... no act of contrition, no recognition of guilt, no stocktaking, no inner reflection shaped by a spirit of soul-searching...”^[78]

Scientists in Germany wanted to quickly move towards normality and forget the past. In view of the fact that, because of the destruction of many institutes and poor material conditions, they continued research and teaching often under difficult conditions, a certain amount of denial and concentration on survival and construction was understandable. However, the fact that the crimes committed by the Germans themselves went more or less unrecognized remains incomprehensible and frightening. Many made Hitler and a few Nazis responsible for these crimes, sometimes they were attributed to human failings in general. A large number of German scientists showed neither feelings of guilt nor of

sorrow, but merely self-pity. One of the reasons was denazification.

After the end of the war a large number of university lecturers were dismissed by the allies’ denazification authorities. Membership of the NSDAP was often sufficient. Many of them were reinstated or retired during the course of the next five years. Even a few political activists were able to become full professors once more. In (bio)chemistry at universities in Germany the remarkable picture was thus formed that amongst the full and associate professors at many German universities at the beginning of the 1950s the proportion of former NSDAP members (for whatever reason they had joined) was often considerably higher than NSDAP members during National Socialism: in West Germany (in (bio)chemistry) in total 53 % of full professors, 70 % associate professors, and 71 % supernumerary professors who held positions at universities at the latest by 1952 were previously members of the NSDAP. At universities in the German Democratic Republic, where denazification was carried out more thoroughly, the proportion of former NSDAP members amongst professors (full professors, professors with teaching duties, or professors with lectureships) was considerably lower at 36 %. The reason that the proportion of previous NSDAP members amongst professors after the war was so high is because during National Socialism a larger percentage of young scientists had organized themselves within the NSDAP. If it is assumed that the situation in other subjects was similar, then German students were taught mainly by former National Socialists after the war.

In contrast to this it must be considered that former Jewish refugees were recalled in only very few cases.^[79] Many of them would not have returned—the large percentage of former National Socialists at universities played a role in this—others, especially the refugees in Turkey, awaited a recall to Germany and under certain conditions would even have returned immediately at the end of the war.^[80] However, they were offered no positions. The fact that neither the Berufsbeamtengesetz (permanent civil servant law) was recognized as an injustice after 1945 nor that deprivation of citizenship was automatically reversed resulted in the effects of the widespread attitude of “forgetting” of the history of the 12 years and the co-responsibility of scientists in the injustice not being brought about during that period.

The post-war correspondence of emigrated chemists and biochemists with their German colleagues makes it clear that to a large extent they looked at the problems of the time solely from a German perspective.^[81] They emphasized the injustice suffered by themselves and presented themselves as victims at the hands of Hitler and the allies as well as their denazification. This attitude interestingly also predominated with the scientists who were not politically incriminated. One example is Otto Hahn (Figure 11). As the discoverer of atomic nuclear fission but

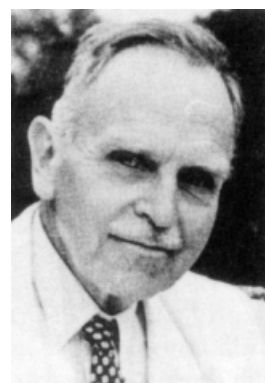


Figure 11. Otto Hahn.

who had not participated in the construction of the atomic bomb and as someone who was known as an anti-Nazi, Hahn embodied the “good” German scientist after 1945. In April 1946 he became president of the Kaiser Wilhelm Gesellschaft (KWG; shortly after the Max Planck Gesellschaft). In his letters to former colleagues in exile the widespread feelings of Germans, who regarded themselves in the first instance as victims, find expression. Furthermore they clearly show his loyalty to the KWG and lack of sensitivity. The absence of self-critical comments and words of sympathy is conspicuous. As Ruth Sime showed in her biography, Lise Meitner suffered under the new nationalism of Hahn, who tried not to mention the past when abroad and to emphasize the injustice that had befallen Germany.^[82]

When Otto Meyerhof, one of the few emigrants who after the war corresponded extensively with former German colleagues on the situation of science in Germany, wrote to Hahn, “*nobody who has found safety here from Nazi persecution can think of returning to a country that has become the graveyard of his nearest and dearest,*”^[83] Hahn replied in an insensitive manner:^[84]

“I can understand that after all that has happened here in Germany to your relatives and close friends that you have no desire (sic) to return here. However, I consider it unjust for those abroad to make the majority of Germans responsible for all the happenings during the last 12 years. If it had been known abroad how great the pressure had been, how it intensified from year to year then one would have a certain understanding that many not very strong characters have simply given up the struggle because they said: we cannot change anything.”

Hahn’s attempt to justify compromise or obedience to the National Socialist regulations does suggest a certain feeling of guilt, and emphasizes the new solidarity between former

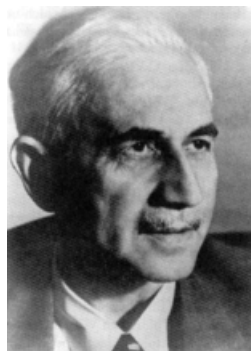


Figure 12. Otto Meyerhof.

Nazis and non-Nazis towards criticism from abroad. Hahn spoke only of political pressure, and thus avoided the active role of the universities and KWG in supporting the anti-Semitic policies.

Meyerhof (Figure 12) was one of the emigrants who spoke out in favor of scientific relationships with overseas researchers being taken up again as soon as possible with the German “anti- and non-Nazis”. He believed there was a right for objective criticism. However, he found as he wrote to Hahn in November 1946 that:

“even the best and most tested of my German friends such as yourself have still not been able to free themselves sufficiently from the narrow field of vision imposed by the Nazis to be able to attribute the new situation prevailing in Germany and Europe to its true roots. Whereas I can fully agree with your complaints on the present situation I depart fully in my interpretation. The interpretation I hold

is that everything which Germany is now experiencing it ‘thanks solely to its Führer’ and that it has itself to thank for its Führer. Germany is not only conquered, that is the least, it has gone through a moral catastrophe, which is without example in history. It has catastrophically devastated the surrounding countries and infected them with its moral disease that now we are in a quandary of how the curse of an evil deed that continually brings forth evil can be prevented. Collective judgments are meaningless. With ‘Germany’ I mean the majority of leading responsible persons.”^[85]

Meyerhof pointed out the difference to France, where in the 1890s a state crisis arose because of a single Jew, Captain Dreyfus. “*When tens of thousands became without rights in Germany in 1933 no one cared, particularly in the universities.*” He recalled the excuses which he heard as he reproached colleagues in Göttingen about the silence of the faculty following James Franck’s resignation, and of that which he experienced in Heidelberg at the time. Meyerhof regarded it as “*unavoidable for the recovery of the spiritual life of Germany*” that not only the 150 % Nazis should be removed from the universities, but also the 75 to 99 %. “*So to say as compensation*” for him and other emigrants standing up for a sensible policy in respect of German science he demanded of Hahn and other non-Nazis that the circumstances in universities be changed and all those who had failed morally be dismissed.

In a short reply, Hahn ensured Meyerhof and “*many other American colleagues*” of his and von Laue’s friendship, but did not go any further into the questions raised.^[86] Instead, Max von Laue, with whom Hahn had discussed Meyerhof’s letter, replied. He agreed with Meyerhof’s judgment that the moralistic collapse in Germany arose because initial resistance (“*Principiis obsta*”) had indeed been possible up to the middle of 1933, but little of it would have been traceable, but he criticized the denazification of the universities, with the exception of political activists, as worse than “*Hitler methods*”.^[87]

Max von Laue was one of the German scientists who during the Nazi era intervened most strongly for Jews, and whom the anti-Jewish measures had affected emotionally. Even he was not ready to understand what a former Jewish refugee must have felt in 1946 when it was explained to him that the methods of the allies (independent of whether they were regarded as legal or appropriate) were worse than the Hitler methods for those involved. Hahn too annoyed former colleagues who now lived as emigrants abroad when during his visit to Sweden to collect his Nobel Prize in 1946 he expressed the opinion that what the Allies were doing in Germany within the framework of denazification was nothing other than what the Germans had done in Poland and Russia.^[88] A few years later, however, von Laue changed his attitude drastically and he became one of the critics not only of the failure of German scientists in 1933, but also of their insincerity after 1945.^[89]

The behavior of Hahn, von Laue, and many other German scientists during the initial post-war years is a reminder of “the sentimentalism, selfishness, self-pity, and the lack of objectivity”, which according to Michael Balfour and John

Mair “tend to characterize a nation in defeat”.^[90] The considerable economic problems in Germany, a narrow nationalistic viewpoint, low sensitivity, and, with Hahn, his new role as President of the KWG (MPG) reinforced this attitude. Such a “forgetfulness” made the cooperation of German National Socialists with those emigrants who would have been willing to aid in the reconstruction of science in Germany impossible, and made normalization of scientific and personal relationships of German scientists with emigrants and colleagues abroad difficult. In particular, former National Socialists had difficulty at first. One example is Adolf Butenandt, who declined a position at Harvard University in 1935; the fact that he had taken over the position of the dismissed Jewish colleague Carl Neuberg as KWI director together with his former membership of the NSDAP made international contacts difficult. For a number of years he was neither invited to international conferences nor did he receive invitations from colleagues in the USA with whom he previously had active exchanges. When during a stay in USA in 1951, the International Union of Chemistry had just decided to accept Germany again as a member Butenandt offered to take part as Germany’s representative at a meeting he received no invitation.^[91]

Many emigrants and scientists from other countries who had suffered under German occupation expected a word of regret to be expressed after the war. One of them was Sir Francis Simon, formerly Professor Franz Simon from Breslau. In 1951 he refused an invitation from Karl-Friedrich Bonhoeffer to take part in a meeting of the Bunsen Gesellschaft with the following reason:^[92]

“There are plenty of scientists in the world and what they have to say can be read. When one goes to a conference one will have the feeling that one is with people of the same mind and not in the society of opportunists. In my opinion German scientists in their totality lost their honor in 1933 and have done nothing to win it back. I admit one can say that it is not to everyone’s liking to risk his position or life, but after the war it was by no means necessary. The least one could have expected after all the misfortune that had been caused was that German scientists in their entirety or through their scientific societies would have said openly and clearly that they regret what had happened. I have not noted any of this—if I am mistaken please correct me.”

Fifty years later, in June 2001, the President of the MPG, Hubert Markl, apologized to the surviving victims for the involvement of the directors and staff of the KWG in the crimes of the Nazi regime.

After 1945, new directions of research which had been founded abroad were taken up with considerable delay in Germany, even when material and technical essentials were available. A decisive reason for this lay in the international isolation and self-imposed isolation of German scientists as a result of the National Socialist past. The expulsion, disenfranchisement, and later murder of European Jews as well as the attempt to bring Europe under the domination of National Socialist Germany by aggression had occurred with the knowledge, the involvement, and the active support of scientists. This past, and the fact that the majority of German

scientists kept silent after 1945, had a negative effect upon international exchange. It thus delayed for years, in part for decades, the reconstruction of specialties which had been greatly weakened as a consequence of the dismissals in 1933 (above all in biochemistry) as well as the development of new interdisciplinary fields, including molecular biology and physical organic chemistry.

I thank Benno Müller-Hill for critical review of the manuscript. The Deutsche Forschungsgemeinschaft has supported this research project through material grant Az Mu 575/8 and by a Habilitationsstipendium, as well as the Sidney Edelstein Foundation by a Fellowship.

Received: 17. September 2001 [A 493]

- [1] A. Schleede to R. Kuhn, March 18, 1938, Material of the GDCh, Frankfurt.
- [2] W. Biltz and G. Tamann to F. Paneth, November 17, 1938, Archives of the MPG, Sect. III/45/121.
- [3] Thus, patents of Jewish chemists in Germany had to appear without names or under other names after 1933. Fritz Haber, who died in 1933, had no obituary in the *Zeitschrift für Angewandte Chemie*, a few other chemical journals, for example, *Berichte der Deutschen Chemischen Gesellschaft* and the *Zeitschrift für Elektrochemie*, did publish obituaries for Haber, but not for other Jewish chemists. The Deutsche Chemische Gesellschaft even exercised restraint in the mention of von Baeyer and Wallach “on order sooner or later not to be open to undesirable reproach” as the managing editor of “Berichte” wrote to the president Richard Kuhn on July 14, 1942 (Material of the GDCh, Frankfurt).
- [4] U. Deichmann, *Flüchten, Mitmachen, Vergessen. Chemiker und Biochemiker in der NS-Zeit*, Wiley-VCH, Weinheim, 2001.
- [5] Chapter 3 in ref. [4].
- [6] Berlin Document Center (now Bundesarchiv (Federal Archive)), REM File W. Prandtl, Gesamturteil der NSDAP-Gauleitung München (Collective Judgment of the NSDAP District Leadership, Munich) of October 19, 1938.
- [7] “Otto Kraymer. October 22, 1899—March 18, 1982”: Avram Goldstein, *Biogr. Mem. Nat. Acad. Sci. USA* **1987**, 57, 151–225; “Otto Kraymer, 22.10.1899 to 18.3.1982 und das ‘Gesetz zur Wiederherstellung des Berufsbeamtentums’ (April 1933)”: U. Trendelenburg, *DGPT Mitteilungen* No. 16, February 1995, 33–34.
- [8] E. Chargaff in conversation with U.D., New York, January 27, 1997.
- [9] Personal communication from Prof. Henning Hopf, August 13, 1999. Fries, after whom the Fries rearrangement is named, insisted that the swastika flag be removed from a laboratory. To remind present day students of Fries and his stance Prof. Hopf named one of the Braunschweig practical laboratories the Fries Hall.
- [10] According to Prof. Hopf after 1933 the TH Braunschweig was particularly thoroughly cleansed because it had refused to appoint Hitler Professor for Political Science (after 1930 the State of Braunschweig had a coalition government of National Socialists and commoners).
- [11] On the discrepancies between performance and too high or too low a number of citations see ref. [4], p. 138. Details on the number of citations of non-emigrated (bio)chemists (p. 230) may also be found there. Names and biographical information of 148 dismissed and/or emigrated (bio)chemists are listed there on pages 118–125 and 134.
- [12] See also D. Nachmansohn, *German-Jewish Pioneers in Science 1900–1933*, Springer, New York **1979**; “Wieviel Zufälliges doch in der Entwicklung steckt. Als die Physiologische Chemie zur Molekularbiologie wurde. Kritisches zur Geschichte der biochemischen Forschung”: L. Jaenicke, in *Wie die Zukunft Wurzeln schlug* (Ed.: R. Gerwin), Springer, Berlin, **1989**; “Paradigmenwechsel und Exodus, Zellbiologie, Zellchemie und Biochemie in Berlin”: Michael Engel in *Exodus von Wissenschaftlern aus Berlin* (Eds.: W. Fischer, K.

- Hierholzer, M. Hubenstorf, P. T. Walther, R. Winau), de Gruyter, Berlin, 1994, pp. 296–341 (Forschungsbericht 7).
- [13] For H. Hellmann, see “Hans G. A. Hellmann (1903–1938). I. Ein deutscher Pionier der Quantenchemie in Moskau”: W. H. E. Schwarz, D. Andrae, S. R. Arnold, J. Heidberg, H. Hellmann, Jr., J. Hinze, A. Karachalios, M. A. Kovner, P. C. Schmidt, L. Züllicke, *Bunsenmagazin* **1999**, 10–21; “Hans G. A. Hellmann (1903–1938). II. Ein deutscher Pionier der Quantenchemie in Moskau”: W. H. E. Schwarz, A. Karachalios, S. R. Arnold, L. Züllicke, P. C. Schmidt, M. A. Kovner, J. Hinze, H. Hellmann, Jr., J. Heidberg, D. Andrae, *Bunsenmagazin* **1999**, 60–70. For information on the effects of the banishment of physicists for chemistry see ref. [4], pp. 154–159.
- [14] a) See the autobiography of Willstätter: R. Willstätters, *Aus meinem Leben. Von Arbeit, Muße und Freunden*, Verlag Chemie, Weinheim, **1949**. b) On the motives for resignation see also F. Litten, *Der Rücktritt Richard Willstätters 1924/25 und seine Hintergründe*, Algorismus: Studien zur Geschichte der Mathematik und Naturwissenschaften, Heft 32, München, **1999**.
- [15] For the scientific influence of emigrants in Turkey see “Die Emigration deutschsprachiger Naturwissenschaftler von 1933–1945 in ihrem sozial- und wissenschaftshistorischen Wirkungszusammenhang”: Regine Erichsen in *Die Emigration der Wissenschaften nach 1933* (Eds.: H. A. Strauss, K. Fischer, C. Hoffmann, A. Söllner), Saur, Munich, **1991**.
- [16] “Hans Stammreich”: B. Schrader, A. Otto, *Bunsenmagazin* **2000**, 120–122. On the emigration to Brazil see R. G. Saidel, G. A. Plonski, *Shaping Modern Science and Technology in Brazil. The Contribution of Refugees from National Socialism after 1933*, Leo Baeck Institute, New York, **1994**, 257–270 (Year Book 39).
- [17] “The Emergence of Biochemistry in Portugal during the Twentieth-Century” I. Amaral, A. M. Nunes dos Santos, R. E. Pinto, Lecture at the XXth International Congress of History of Science, **1997**.
- [18] M. von Stackelberg to the German Legation in Cairo, September 12, 1938 (personal file of von Stackelberg, University Archive, Bonn).
- [19] Letter of the Reichserziehungsministeriums of September, 28, 1938 (personal file of von Stackelberg, University Archive, Bonn).
- [20] Judgment of September 15, 1949 (personal file of von Stackelberg, University Archive, Bonn).
- [21] “Alexander Schönberg 1892–1985”: E. Singer, *Chem. Ber.* **1987**, 120, III.
- [22] “Alexander Schönberg 1892–1985”: E. Singer, *Chem. Ber.* **1987**, 120, I.
- [23] Further literature and source information are found in ref. [4], pp. 128–129.
- [24] On Fritz Haber, see a) D. Stoltzenberg, *Fritz Haber. Chemiker, Nobelpreisträger, Deutscher, Jude*, VCH, Weinheim, **1994**, and b) M. Szöllösi-Janze, *Fritz Haber 1868–1934. Eine Biographie*, Beck, München, **1998**.
- [25] Chapter 2 in ref. [4]. For Wieland’s political stance, see “Chemiker im Gespräch: Erinnerungen an Heinrich Wieland”: H. Hamm-Brücher and G. Freise, *Chem. unserer Zeit* **1977**, 11, 143–149; “Erinnerungen an Heinrich Wieland (1877–1957)”: B. Witkop, *Liebigs Ann. Chem.* **1992**, I-XXXII; “Heinrich Wieland hundert Jahre: Sein Werk und Vermächtnis heute/Heinrich Wieland Centennial: His Lifework and His Legacy Today”: B. Witkop, *Angew. Chem.* **1977**, 89, 575–589, *Angew. Chem. Int. Ed.* **1977**, 16, 559–572. For Straßmann’s political stance during the NS era, see F. Krafft, *Im Schatten der Sensation. Leben und Wirken von Fritz Straßmann*, Verlag Chemie, Weinheim, **1981**, pp. 40–46. Straßmann is the only German chemist honored with a tree in the Avenue of the Righteous, in Yad Vashem, Jerusalem.
- [26] I am not aware whether anyone employed these co-workers beyond the officially allowed deadline.
- [27] Berlin Document Center, now Bundesarchiv, REM File Windaus, Windaus to the REM, November 2, 1935.
- [28] Cited according to: B. Müller-Hill, *Erinnerung und Ausblendung. Ein kritischer Blick in den Briefwechsel Adolf Butenandts*, MPG Präsident 1960–1972, **2001**. There is no reply of Butenandt in his papers.
- [29] a) See R. Havemann, *Fragen, Antworten, Fragen. Aus der Biographie eines deutschen Marxisten*, Piper, Munich **1990** especially pp. 81–92 (new edition); b) “Robert Havemann—eine deutsche Biographie”: D. Hofmann, Epilogue to ref. [29a].
- [30] Ref. [29a], p. 83.
- [31] “Dem Vaterlande—solange es dies wünscht. Fritz Habers Rücktritt 1933, Tod 1934 und die Fritz-Haber-Gedächtnisfeier 1935”: U. Deichmann, *Chem. unserer Zeit* **1996**, 30, 141–149.
- [32] See chapter 2.3.2 in ref. [4]. Helmut Behrens, who during National Socialism was active as a student and lecturer in chemistry at the TH Munich, remembers that the anti-Jewish measures including deportation were visible to all, but only a few of his colleagues were affected by them. (“Wissenschaft in turbulenter Zeit: Erinnerungen eines Chemikers an die Technische Hochschule München 1933–1953”: *Algorismus—Studien zur Geschichte der Mathematik und Naturwissenschaften*, vol. 25, Münchener Universitätschriften, Munich, **1998**, p. 64.)
- [33] Karl Freudenberg to George Barger, July 17, 1933, K. Freudenberg-Nachlass, Universitätsarchiv Heidelberg, Rep. 14/111.
- [34] Ref. [33].
- [35] S. Friedlander in *Nazi Germany and the Jews, Vol. I*, HarperCollins, New York, **1997**, p. 56.
- [36] For Ostwald see Section 2.3, for Freudenberg, Harteck and Bonhoeffer see chapter 2.3.1 in ref. [4]. Harteck refused to intercede for his dismissed colleagues, the Jewish assistants of the KWI for Physical Chemistry; he himself profited from the dismissals in that he took over the position of Otto Stern as Professor for Physical Chemistry in Hamburg. Bonhoeffer did not criticize the dismissals as such, merely the way in which they were carried out. For Havemann, see ref. [24b], pp. 669–673. For unknown reasons Havemann denounced the already dismissed or resigned scientists of the KWI for Physical Chemistry—Haber, Freundlich, Kallmann, Polanyi, and Söllner—in the summer of 1933 because of allegedly intended incorrect business practices at the Prussian Ministry for Education.
- [37] “German Scientists and Hitler’s Vendetta against the Nobel Prizes”: E. Crawford, *Hist. Stud. Phys. Sci.* **2000**, 31, 37–53.
- [38] “Über manchmal bestehende Schwierigkeiten, einen Chemie-Nobelpreis entgegenzunehmen”: A. Neubauer, Lecture at the Annual Congress of the GDCh in Würzburg, September 24, 2001.
- [39] A. Ellmer to R. Kuhn on May 28, 1943, Material of the GDCh, Frankfurt, regarding the publication of articles by Jews.
- [40] H. Kretschmar to H. Hörlein on April 23, 1933, Archive of the GDCh, Frankfurt.
- [41] For biology, see U. Deichmann, *Biologists under Hitler*, Harvard University Press, Cambridge, **1996**, chap. 2, for chemistry and biochemistry, see chapter 5 of ref. [4].
- [42] W. Ostwald to the DFG on May 2, 1937, Bundesarchiv Koblenz (BAK), R73/13500.
- [43] a) See B. Müller-Hill, *Murderous Science. Elimination by Selection of Jews, Gypsies, and Others, Germany 1933–1945*, Oxford University Press, Oxford, **1988**. Details on the current state of knowledge may be found in the article “Das Blut von Auschwitz und das Schweigen der Gelehrten”: B. Müller-Hill in *Geschichte der Kaiser-Wilhelm-Gesellschaft*, vol. 1 (Ed.: Doris Kaufmann), Wallstein, Göttingen, **2000**, pp. 189–227.
- [44] *Angew. Chem.* **1933**, 46, 789.
- [45] Obtained from records and material on the Verein deutscher Chemiker written and collected by Dr. H. Ramstetter. They are located at the offices of the GDCh. See also W. Ruske, *100 Jahre Deutsche Chemische Gesellschaft*, Verlag Chemie, Weinheim, **1967**, p. 152.
- [46] Ref. [44].
- [47] R. Havighurst, Rockefeller Foundation, October 6, 1947, Rockefeller Archive Center, Collection RF, RG 1.1/717 box 3, folder 19.
- [48] For research support in (bio)chemistry see chapter 5 in ref. [4].
- [49] Chapter 7 in ref. [4]; The Fraud of Abderhalden’s Enzymes“ U. Deichmann, B. Müller-Hill, *Nature* **1998**, 393, 109–111, see also “Sensation, Irrtum, Betrug?—Emil Abderhalden und die Geschichte der Abwehrfermente“: M. Kaasch, *Acta Historica Leopoldina*, **2000**, 36, 145–200.
- [50] In the budget of the medical branch of the des Reichsforschungsrats, for example, for the year 1938/39 cancer research was supported with considerably higher sums than general medicine and general genetic and race research (BAK, R73/12388, Etat der Fachsparte Medizin 1938/39; Kostenvoranschlag für das Rechnungsjahr 1937/38 für das Arbeitsprogramm auf dem Gebiet der Tumorforschung).
- [51] Berlin Document Center (today Bundesarchive) REM File E. Walschmidt-Leitz.

- [52] A comprehensive presentation on “German chemistry” is found in “*Deutsche Chemie*”. *Der Versuch einer deutschartigen, ganzheitlich-gestalthaft schauenden Naturwissenschaft während der Zeit des Nationalsozialismus*. M. Vonderau, Dissertation, Marburg, **1994**.
- [53] a) G. Gellermann, *Der Krieg, der nicht stattfand*, Bernard & Graefe, Koblenz, **1986**; b) “Die deutschen Gaskriegsvorbereitung 1919–1945”: R. D. Müller, *Militär-geschichtliche Mitteilungen* **1980**, *1*, 25–54. I.G. Farben also worked—unsuccessfully—on the development of an effective protective filter against nerve gases. The absence of such a protection played an important role in the decision of Hitler and the army in the end not to use chemical weapons. According to Gellermann (ref. [53a], p. 208) other aspects were: the chemical groups of the army, the support troops, were still in their infancy in 1939. Later it was hardly possible to withdraw regiments from the front and to convert them into chemical warfare and defense units which would have been necessary for gas warfare. With the defeat of the Luftwaffe, the most important possible means of deployment of gas warfare agents was finally lost.
- [54] Goebbels to Thiessen on September 3, 1936, Archive of MPG, I/1A, 1174.
- [55] Thiessen to Telschow on May 4, 1940, Archive of MPG, I/1A, 1175.
- [56] See chapter 5 in ref. [4].
- [57] a) Georg Graue to Schröder KWG, July 20, 1951. According to Graue, a former co-worker of Thiesse, co-workers and materials were sent there but the work could no longer be started because it was too late; b) see also “Der Physikochemiker Peter Adolf Thiessen als Wissenschaftsorganisator (1899–1990)”: C. Eibel, Dissertation, Historisches Institut der Universität Stuttgart, **1999**.
- [58] Interrogation of R. Kuhn, April 1–2, 1946 at KWI for Medical Research, BIOS Final Report 542, Item No. 8, Imperial War Museum London, Dept. of Documents; R. Kuhn to Dr. Baumann, September 5, 1945, Archive of MPG, I/29/143; Professor Dr. L. Birkofer, Düsseldorf, April 11, 1994, and Prof. Dr. O. Dann, Eberbach, April 13, 1994, in conversation with UD.
- [59] Interrogation of K. Brandt, BIOS Final Report 542, Item No. 8, Imperial War Museum London, Dept. of Documents. According to the information of Kuhn’s co-worker Otto Dann, Kuhn expressed in these conversations his worry about the helplessness in protecting his own people in the event of an allied gas attack. (O. Dann in conversation with UD, April 13, 1994).
- [60] E. Chargaff in conversation with UD, New York, January 28, 1997.
- [61] O. Meyerhof to Richard Kuhn, November 1, 1945, Meyerhof papers, Archives University of Pennsylvania.
- [62] See, for example, Peter Hayes, *Industry and Ideology. I.G. Farben in the Nazi Era*, Cambridge University Press **1987** and Joseph Borkin, *Die unheilige Allianz der I.G. Farben. Eine Interessengemeinschaft im Dritten Reich*, Campus, Frankfurt/M **1981**.
- [63] See ref. [41], chapter 3.3.
- [64] The first critical analysis of the past of human genetics by an anthropologist came from (Karl Saller, *Die Rassenlehre des Nationalsozialismus*, Progress Verlag, Darmstadt, **1961**), by a geneticist from Benno Müller-Hill (ref. [43a]).
- [65] M. Walker, *Die Uranmaschine. Mythos und Wirklichkeit der deutschen Atombombe*, Siedler, Berlin **1990**.
- [66] a) The protocols are published in: *Operation Epsilon. Die Farm-Hall-Protokolle oder die Angst der Alliierten vor der deutschen Atombombe* (Ed.: D. Hoffmann), Rowohlt, Berlin **1993**; the protocols clearly show that the refusal to construct the atom bomb for moral or political reasons is not discussed; b) the book appeared with a supplement to the introduction by D. Cassidy as *History of Modern Physics and Astronomy, Vol. 1*, Springer, Heidelberg, **1996**.
- [67] An early example is Otto Köhler, *„und heute die ganze Welt. Die Geschichte der I.G. Farben und ihrer Väter*, Rasch und Röhrig, Hamburg, **1980**.
- [68] R. Pummerer, *Angew. Chem.* **1949**, *61*, 395. Although Willstätter’s resignation in 1925 as a protest against anti-Semitism and his emigration in 1939 “because of the Hitler persecution of Jews” was mentioned, there are no passages in which Willstätter took issue with the behavior of his colleagues during the Nazi era. The journal printed a few pages of Willstätter’s book in the same edition as a memorandum to Richard Willstätter. The innocuous chapter “*Extraordinarius in München 1902–1905*” was chosen.
- [69] *Angew. Chem.* **1950**, *62*, 131–132.
- [70] K. Freudenberg to P. Karrer, December 8, 1947, Freudenberg-Nachlaß, University archive, Heidelberg, Rep. 14/212.
- [71] C. Krauch from the Nuremberg prison to K. Freudenberg June 25, 1948. P. Karlson, *Adolf Butenandt. Biochemiker, Hormonforscher, Wissenschaftspolitiker*, Wissenschaftliche Verlagsanstalt, Stuttgart, **1990**, pp. 149–151.
- [72] “Das Nürnberger Urteil im Chemieprozeß”: O. Gerhardt, *Phys. Bl.* **1948**, *4*, 429.
- [73] Cited according to ref. [72].
- [74] For example, in P. Levi, *Ist das ein Mensch? Erinnerungen an Auschwitz*, Fischer, Frankfurt, **1961**; P. Levi, *Die Untergegangenen und die Geretteten*, Hanser, Munich, **1990**.
- [75] Cited according to ref. [72].
- [76] The leading I.G. representatives, particularly the director of the Bayer-Werke Heinrich Hörlein, were incensed by this passage. Hörlein spent many months in discussion with his colleagues at Bayer on possible actions, and he put pressure—without success—on the publisher of the book (Arthur Stoll) and *Angewandte Chemie*, to persuade them to publish a counter-response. See “The Richard Willstätter Controversy: The Legacy of Anti-Semitism in the West German Chemical Industry”: J. Wiesen in *The German Chemical Industry in the Twentieth Century* (Ed.: J. E. Lesch), Kluwer Academic Publishers, Dordrecht, **2000**, pp. 347–366.
- [77] E. Verg, G. Plumpe, H. Schultheis (Ed.: Bayer AG), *Meilensteine*, Informedia-verlags-gmbh, Leverkusen, **1988**, p. 298.
- [78] W. Jens, *Eine deutsche Universität. 500 Jahre Tübinger Gelehrtenrepublik*, Kindler, Munich, **1977**, pp. 342–343.
- [79] Jewish refugees amongst the chemists who were called back to university teaching positions prior to their retirement were Stefan Goldschmidt (1946, Professor for Organic Chemistry at the TH Munich), Hans Kröpelin (1946, TH Braunschweig), Walter Fuchs (1949, Professor for Technical Chemistry at the TH Aachen), and Georg-Maria Schwab (1950, Professor for Physical Chemistry at Munich University). The following chemists returned to Germany after their age-related retirement: Friedrich Paneth (1953), Fritz Arndt (end of the 1950s), and Alexander Schönberg (1957).
- [80] A list with the names of 24 university teachers in Turkey who in 1946 were willing to return to Germany is found in a letter from F. Breusch to O. Meyerhof, January 14, 1946, Meyerhof papers, University of Pennsylvania.
- [81] I refer in the main to correspondence in the papers of emigrated Jewish scientists and non-emigrated German scientists as well as to personal interviews with chemists and biochemists.
- [82] a) R. L. Sime, *Lise Meitner, A life in Physics*, University of California Press, Berkeley, USA, **1996**, p. 345; b) see also R. L. Sime, *Angew. Chem.* **1991**, *103*, 956–967; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 942–953.
- [83] O. Meyerhof to O. Hahn, June 25, 1946, Otto Hahn papers, Archive of the MPG, Rep. III/14A.
- [84] O. Hahn to O. Meyerhof, June 5, 1946, Otto Meyerhof papers, University of Pennsylvania, Philadelphia, Archives.
- [85] O. Meyerhof to O. Hahn, November 8, 1946, Otto Hahn papers, Archive of the MPG, Rep. III/14A.
- [86] In letters to colleagues in Germany, Hahn expressed concern on the large number of active Nazis in universities, a concern which he did not communicate with his colleagues in exile. Thus, he questioned Klaus Clusius, Dean of the natural Science Faculty of the University of Munich, in a letter of May 4, 1946 as to how far it was true that a large percentage of active National Socialists were again working at this university (Otto Hahn papers, Archive of the MPG, III/14A).
- [87] M. von Laue to O. Meyerhof, December 24, 1946, Otto Meyerhof papers, University of Pennsylvania.
- [88] Ref. [82a], p. 345.
- [89] Ref. [82a], p. 364.
- [90] M. Balfour, J. Mair, *Four-Power Control in Germany and Austria*, Oxford University Press, London, **1956**.
- [91] A. Butenandt to K. Freudenberg, November 28, 1951, Freudenberg Estate, University Archive Heidelberg.
- [92] F. Simon to K.-F. Bonhoeffer, March 22, 1951, Archives of the MPG, K.-F. Bonhoeffer papers.

Dendritic Polymers in Biomedical Applications: From Potential to Clinical Use in Diagnostics and Therapy

Salah-Eddine Stiriba, Holger Frey,* and Rainer Haag*

Dendrimers are characterized by a combination of high end-group functionality and a compact, precisely defined molecular structure. These characteristics can be used in biomedical applications, for example, for the amplification or multiplication of effects on a molecular level, or to create extremely high local concentrations of drugs, molecular labels, or probe moieties. A brief summary of the current state of the art in the field is given, and focuses on the application of dendrimers both in diagnostics as well as in therapy. In diagnostics, dendrimers that bear Gd^{III} complexes are used as contrast agents in magnetic resonance imaging. DNA dendrimers have potential for routine use in high-throughput functional genomic analysis, as well as for DNA biosensors. Dendrimers are also being investigated for therapeutics, for example, as carriers for controlled drug delivery, in gene transfection, as well as in boron neutron-capture therapy. Furthermore, the antimicrobial activity of dendrimers has been studied.

1. Introduction

Dendrimers are perfectly cascade-branched, highly defined macromolecules, characterized by a combination of high end-group functionality and compact molecular structures. Since the seminal works in this field,^[1] a large number of dendrimer structures have been developed and has become a subject of intense interdisciplinary research efforts, bringing together scientists from entirely different areas. The perfectly branched, monodisperse structure of dendrimers have established them as valuable model compounds to study fundamental electrochemical, photophysical, and supramolecular properties.^[2]

[*] Priv.-Doz. Dr. H. Frey, Dr. R. Haag, Dr. S.-E. Stiriba
Institut für Makromolekulare Chemie
und Freiburger Materialforschungszentrum (FMF)
Universität Freiburg
Stefan-Meier-Strasse 21/31, 79104 Freiburg (Germany)
Fax: (+49) 761-203-4709
E-mail: holfrey@fmf.uni-freiburg.de
Haag@fmf.uni-freiburg.de

Based on the rapid advances in this area over the past 15 years, the quest for practical applications for dendrimers is becoming increasingly intense. Owing to the tedious stepwise synthetic construction of dendrimers, future applications will have to be highly specific and a precise nanoengineered structure will be a crucial prerequisite for the targeted application. Bulk applications, for example, as processing additives, specialty coatings, or as rheology modifiers will be realized with random cascade-branched hyperbranched materials, which are structurally less defined but can be prepared in a single polymerization step.^[3]

The structural precision of dendrimers has motivated numerous studies aimed at biomedical applications, for example, the amplification of molecular effects or the creation of extremely high local concentrations of drugs, molecular labels, or probe moieties. In this brief account, we summarize the current state of the art in the field of medical application of dendrimers and highlight the most promising recent developments.

2. Medical Diagnostics

Magnetic resonance imaging (MRI) is a powerful technique in modern medical diagnostics^[4] and is used to visualize soft tissue, for example, organs and blood vessels. MRI is based on subtle differences of environment-sensitive ¹H NMR resonances (mainly of H₂O) in living systems, enhanced by the administration of a paramagnetic contrast agent. The contrast agents (most widely approved for clinical use are Gd^{III} complexes such as [Gd(DTPA)]²⁻, [Gd(DOTA)]⁻ (Dotarem), [Gd(HP-do3a)] (Prohance)^[5]) serve to modify the T₁-relaxation rate of protons in the H₂O molecules and thus the quality of visualization.^[6a] Crucial properties of Gd^{III} complex based MRI contrast agents include good biocompatibility of the chelating ligands, lower toxicity than the corresponding metal salts, and high relaxivity.^[7] Furthermore, excellent solubility and a low dose requirement for diagnosis (0.1–0.001 mg kg⁻¹) as well as good excretion of the complexed metal ions from the biological system in combination with high thermodynamic and kinetic stability are important requirements for MRI contrast agents. A major drawback of currently used low molecular weight contrast agents is their rapid diffusion into the extracellular matrix and consequently fast elimination from the blood circuit. This necessitates

relatively high doses and injection rates. Attachment of low molecular weight Gd^{III} chelates to linear macromolecules such as polylysine and poly(ethylene glycol) (PEG) and also to polysaccharides has been explored. However, the relaxivities of these polymers were low and independent of temperature at all field strengths, which was ascribed to the flexibility and segmental mobility within the polymer chain or the spacer arms.^[6b]

In pioneering work, Wiener et al. reported dendrimer-based Gd^{III} chelates that consist of polyamidoamine (PAMAM) dendrimers of generations 2 and 6 ([G2] and [G6]), which possess 12 and 192 reactive terminal amines, respectively, conjugated to the chelating ligand 2-(4-isothiocyanatobenzyl)-6-methyldiethylenetriaminepentaacetic acid (dtpa) through a thiourea linkage (Figure 1).^[8] In vivo experiments

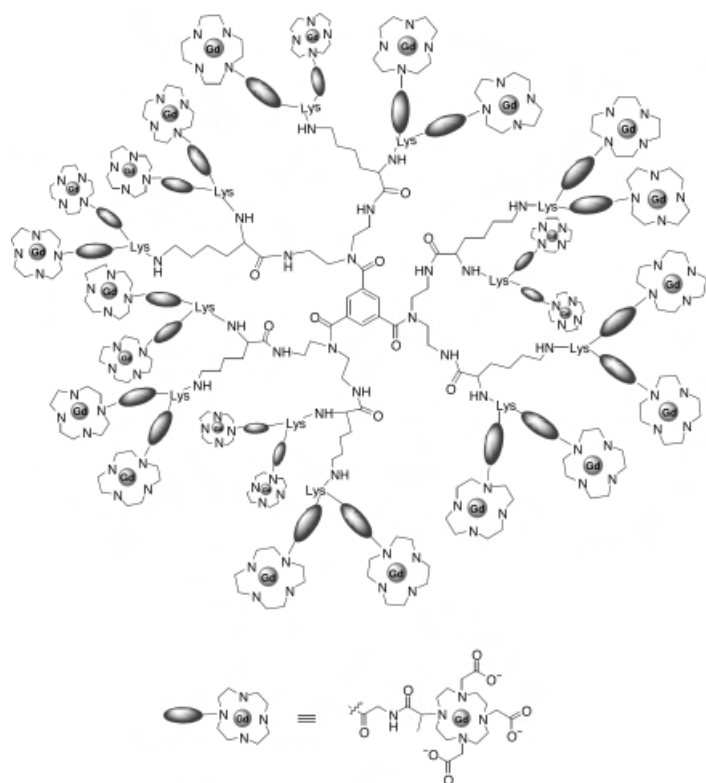


Figure 1. Structure of the dendritic Gd complex gadomer 17,^[11] which is employed in MRI.

on rabbits showed excellent MRI images of blood vessels and long blood circulation times (>100 min) upon intravenous injection of larger dendrimer conjugates, for example, [G6]-PAMAM-TU- Gd^{III} -dtpa. These results are further confirmed by recent studies in which even larger PAMAM dendrimers ([G9] and [G10]) were used.^[9a] In this case, although a saturation of relaxivity was observed per Gd ion with dendrimer generation, the total molecular relaxivity increased strongly. A linear increase in the relaxivity as a function of molecular weight was also found in another study, which demonstrated prolonged half-lives of dendrimer polychelates from [G3] to [G5] in blood. These dendrimer polychelates were exploited for high-quality MR angiography (MRA) images up to 60 minutes post injection. Another feature of

these MRI dendrimers is the retention of up to 40% of larger derivatives in the liver seven days after administration. Upon incorporation of PEG subunits into Gd^{III} -chelated PAMAM dendrimers, liver retention after seven days decreased to 1–7%.^[9b] Further studies that confirm these trends have been reported, and emphasize the importance of the lowered water exchange rates for PAMAM-based Gd contrast agents.^[10]

The potential of this application area is mirrored in the intense efforts by pharmaceutical companies to introduce such contrast agents. For example, the 24- Gd -dtpa cascade polymer and gadomer 17 (Figure 1) have been introduced.^[11] These compounds consist of a trimesic acid central moiety with [G2]-polylysine dendron substituents that bear 24 dtpa and 24 do3a chelating groups, respectively.

Gadomer 17 is suitable for blood-pool imaging (Figure 2), similar to the known linear Gd -dtpa-polylysine, but shows a superior elimination rate, presumably as a result of the globular nature of the dendrimer derivative.^[12a] This



Figure 2. Contrast-enhanced magnetic resonance image of the peripheral blood vessels of a dog after injection with gadomer 17 (dose: $50 \mu\text{mol per kg}$ body weight; ≈ 3 min post injection).

dendrimer-based contrast agent also extends the temporal window of dynamic contrast-enhanced MRI,^[12] as confirmed in several recent pharmacokinetic studies of gadomer 17 and related compounds.^[13] Clinical trials (phase I) are currently underway. A recent alternative approach is based on the utilization of a glycodendrimer framework that is anchored to dtpa as functionalized ligands and in which the Gd^{III} ions are coordinated at the center of the dendrimers.^[14]

Another interesting field is the investigation of DNA dendrimers,^[15] which are constructed by sequential hybridizations of partially complementary heteroduplexes ("DNA monomers"). After each generation, the structure is fixed by a "crosslinking" step. DNA dendrimers with up to two million terminal oligonucleotide strands have been reported. These DNA dendrimers (commercialized as 3DNA-technology^[16]) offer numerous possibilities for oligonucleotide detection,

since the terminal polynucleotide strands can be varied and also be labeled with hundreds of radioactive or fluorescent labels (Figure 3), thus leading to enhanced detection sensitivity. Such DNA dendrimers have been used to identify oligonucleotides directly in chick embryo tissue and also as a specific probe to detect the Epstein–Barr virus in post-transplant patients by recognition of specific RNA strands.^[17] Polynucleotide dendrimers with fluorescent labels have also been used for signal amplification in DNA microarray technology, and are promising candidates for routine use in high-throughput functional genomic analysis.^[18]

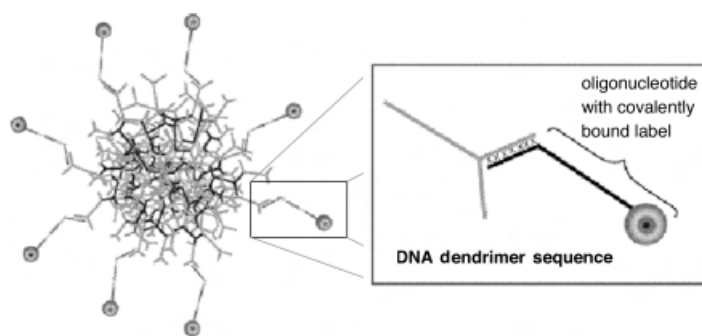


Figure 3. Multifunctional DNA dendrimers with multiple fluorescent labels are used for DNA hybridization and sensor applications.^[16]

Biosensors for DNA hybridization hold great promise for the rapid diagnosis of genetic and pathogenetic diseases. Such sensors rely on the immobilization of single-stranded oligonucleotide probes that selectively recognize their complementary target sequence through hybridization. Biosensors based on a quartz-crystal microbalance and on DNA dendrimers make use of the increased hybridization capacity and detection capability of polyfunctional DNA molecules and have been shown to exhibit significantly enhanced sensitivity in combination with very low detection limits.^[19]

In a similar manner, radiolabeled monoclonal antibodies with high specific activity have been prepared by attachment of PAMAM dendrimers loaded with ¹¹¹In or ¹⁵³Gd complexes.^[20] A further concept for DNA detection was introduced by Fréchet and co-workers and is based on the antenna effect of a dendronized polymer with a single DNA strand at the core. The dendritic architecture is equipped with dye molecules on each dendritic arm, which transfer their energy to a complementary fluorescently labeled DNA strand upon hybridization.^[21]

3. Therapeutic Applications

The most active area in dendrimer-based therapeutics is gene transfection by dendrimers as nonviral vectors. Polyamine dendrimers such as PAMAM and poly(propylene imine) (PPI) are commercially available and their complexation to DNA molecules has been studied.^[22] In particular, their tendency to form compact polycations under physiological conditions (pH 7.4) has been used in gene therapy.^[23] For instance, PolyFect is a commercially available *in vitro* transfection agent and is based on a dendritic PAMAM structure obtained by partial chemical hydrolysis of PAMAM dendri-

mers.^[23b,24] Under physiological conditions, the branches bear positively charged ammonium end groups, which can interact with negatively charged phosphate groups of nucleic acids. The PolyFect reagent assembles DNA into compact toroidal structures, thus optimizing the entry of the DNA into cells. Once inside the cell, the dendrimers buffer the lysosomes after fusion with the endosomes (Figure 4). This leads to pH-controlled inhibition of lysosomal nucleases, thus ensuring the high stability of PolyFect–DNA complexes. However, the final penetration into the nucleus of the cell and the elimination of these cationic macromolecules are not fully understood yet.

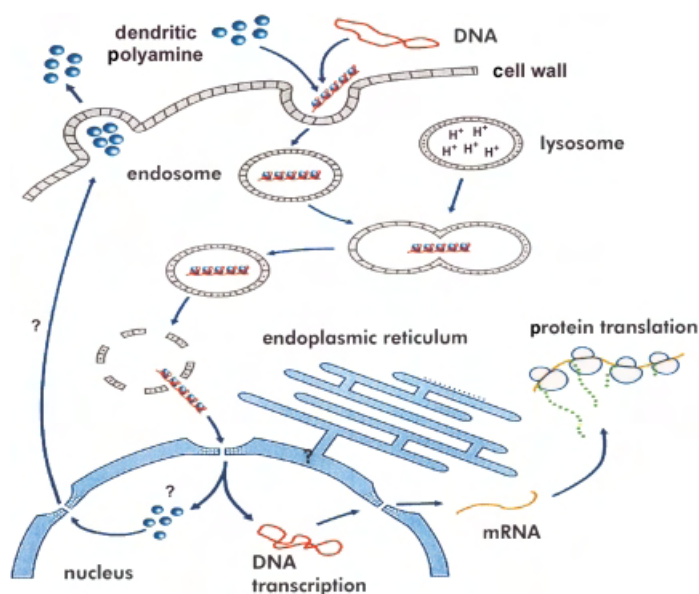


Figure 4. Hypothetical mechanism of DNA transfection with cationic dendrimers.^[24,25]

Interestingly, the perfect dendritic structure (DB = 100%) is a less effective transfection agent than the partially degraded (hyperbranched) structure that results from the partial cleavage (hydrolysis) of the branches.^[23] This observation is also supported by the fact that the commercially available poly(ethylene imine), which is a hyperbranched polymer (DB ≈ 65%), is also an efficient transfection agent.^[25] However, it is still not clear whether these dendritic polyamine transfection agents can be employed *in vivo*, and further toxicity studies are required.^[26] Only in cancer therapy with an Epstein–Barr virus-based plasmid vector complexed to a PAMAM dendrimer was a significant prolongation of survival observed in an animal model.^[27]

Another area of current dendrimer research efforts is controlled drug delivery.^[28] Topological encapsulation within dendrimers has been suggested as a means to transport drugs (Figure 5). Meijer and coworkers first reported the encapsulation of polar guest molecules into a dendritic core-shell architecture with a dense apolar shell, the so-called “dendritic box”.^[29] Depending on their molecular weight, guest molecules can be encapsulated and selectively released from this dendritic host.^[30] The problem of this and similar systems^[31] for drug delivery, however, is their high hydrophobicity. More recently, water-soluble drug-delivery systems with reversed

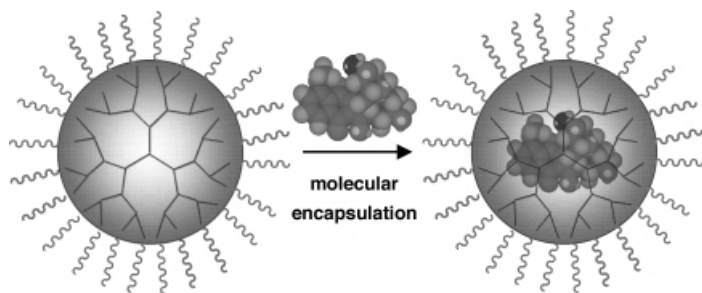


Figure 5. Schematic representation of the encapsulation of the cytostatic adriamycin in a PAMAM dendrimer with PEG end groups.

core-shell polarity based on dendritic polymers have been developed.^[32] Thus antitumor cytostatics such as adriamycin and methotrexate have been encapsulated in such dendrimers (Figure 5).^[32a]

Owing to their high surface functionality, dendritic polymers, particularly dendritic glycopolymers, have also been considered as scaffolds for polyvalent drugs.^[33] Various dendrimer structures with multiple carbohydrate moieties attached at the periphery have been investigated. The so-called “sugar-coating” of dendrimers serve as multivalent recognition structures for sugar-binding proteins, for example, lectins.^[34] For example, poly(L-lysine) dendrimers with two to 16 sialic acid units show enhanced binding affinities in the *Limax flavus* lectin precipitation assay and in the hemagglutination assay of erythrocytes, which tests for the influenza A virus.^[35] In these systems, four to six sialic acid residues appeared to be the optimal number of functional groups for the most potent antiviral properties (ca. 200-fold increase in binding affinity relative to the monovalent ligand), probably as a result of the restricted accessibility of the end groups of higher functional dendrimers. Recently, a pentavalent starlike carbohydrate ligand has been reported to fit exactly into the binding pocket of the five subunits of the Shiga-like bacteria toxin (a close analogue of the cholera toxin).^[36] The binding affinity of this pentavalent ligand is 10^7 times higher than that of the monovalent ligand.

Boron neutron-capture therapy (BNCT) is yet another therapeutic application of multifunctional dendritic macromolecules and has been used in the treatment of cancer. This method is based on the $^{10}\text{B}(n,\alpha)^7\text{Li}^{3+}$ reaction. If ^{10}B can be delivered in sufficient quantities ($>10^9$ ^{10}B atoms) to the tumor tissue, subsequent irradiation with thermal or epithermal neutrons produces highly energetic α particles and $^7\text{Li}^{3+}$ ions that damage the mitotic potential of the tumor cells.^[37] A central issue for BNCT is the precise localization of the boron-containing therapeutics in the tumor. BNCT has been improved by using caged sulfhydryl borohydrides such as $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$. For applications in BNCT, the reagents must have a tumor/blood partition ratio at least greater than 1 (and preferably higher during the radiation process) and the compounds used should have a low toxicity.^[37]

The incorporation of boron into polymer scaffolds represents a promising concept to enhance the activity of boron compounds in order to target a large quantity of ^{10}B in the tumor tissue. PAMAM dendrimers have been used to prepare boron-containing immunoconjugates to give high concentra-

tions of boron. [G2] and [G4] PAMAM dendrimers were linked to the isocyanatoborane $\text{Na}(\text{CH}_3)_3\text{NB}_{10}\text{H}_8\text{NCO}$. This compound was attached to monoclonal antibodies to give an immunoconjugate for selective tumor targeting (Figure 6). The immunoconjugate retained a high level of immunoreactivity, and had a strong propensity to localize in the liver and spleen.^[38]

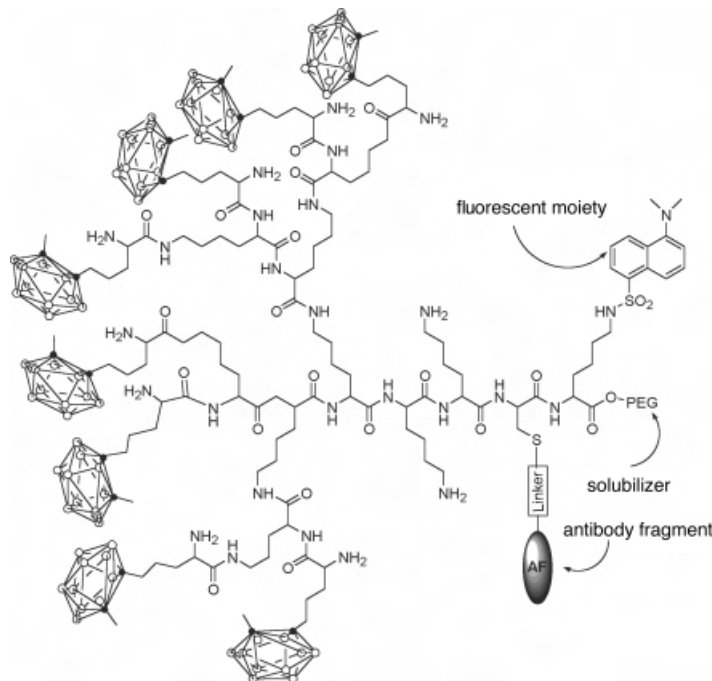


Figure 6. Multifunctional dendrimer conjugate linked to a specific antibody fragment, used in boron neutron-capture therapy (BNCT).

Tests of polylysine dendrons with 80 terminal boron atoms and linked to antibody fragments also revealed promising perspectives for applications in BNCT.^[39] To achieve more effective tumor targeting with antibodies, the Epidermal Growth Factor (EGF), a single small polypeptide, was attached to a boronated [G4]-PAMAM dendrimer. In vitro studies with these bioconjugates indicated a specificity for the EGF receptor (EGFR) in brain tumors.^[40]

Dendrimers with antimicrobial properties represent another facet of dendrimers in medicine. The enhanced interaction of dendritic polycations with cell walls can also be used to generate antimicrobial activity. Quaternary ammonium compounds (QACs) are widely used as disinfectants. Permanent polycationic structures have also been prepared by quaternization of polyamine dendrimers, for example, PPI dendrimers functionalized with dimethyldodecylammonium groups show strong antimicrobial activity.^[41] Bioluminescence studies confirmed that these dendrimer biocides with 16 QAC groups on the surface are two orders of magnitude more potent against the Gram-negative bacteria, *Escherichia coli* than the monofunctional counterparts, and are also very effective against Gram-positive bacteria, such as *Staphylococcus aureus*.^[42] The polycationic structure facilitates the initial adsorption of the dendrimers at the cell wall and increases the permeability of cells towards foreign molecules. It was demonstrated that the

antimicrobial activity depends on the dendrimer generation, the length of the hydrophobic group, and the counterion present.^[42]

Dendrimer–silver complexes and nanocomposites prepared on the basis of dendrimer templates show greater in vitro activity than silver nitrate against various bacteria.^[43] In contrast to silver nitrate solutions, the dendrimer–silver nanocomposites do not penetrate through membranes and might be useful for the antimicrobial treatment of topical wounds, such as burn wounds.

4. Conclusion

It is clear from the examples presented in this highlight that the unique structural features of dendrimer architectures have been used in medical applications in recent years. An increasing number of publications in medical journals have demonstrated the awareness and growing interest in these macromolecules in the medical community, both for advanced diagnostic tools as well as for therapeutic purposes. Progress has been made in MRI as well as in dendritic DNA for biosensor technology. In comparison, therapeutic application lags behind; however, efforts devoted to in vivo applications are long-term projects that require extensive testing and screening procedures with respect to toxicity, immunogenicity, and biodistribution.^[44]

A central issue in this field will be a critical discussion concerning structural requirements: since most applications rely mainly on the high end group functionality of dendrimers and *not* on their unique structural perfection, randomly branched dendritic represent a promising alternative.^[3] Although it has been demonstrated that the structural perfection of dendrimers is an important prerequisite for magnetic resonance imaging, a monodisperse structure may not be required for numerous other applications. Recently, novel biodegradable and biocompatible hyperbranched polymers that offer additional potential in this rapidly growing field have been developed, for example, polyaminoesters^[45] and polyglycerol.^[46] Since dendritic molecules have “infected” the medical community, further interdisciplinary research efforts and eventually new strategies for medical diagnostics and therapy are guaranteed. Since the submission of this Minireview further work on this theme has been reported.^[47]

We thank Dr. H. Schmitt-Willich (Schering AG), Dr. M. Weber (Qiagen GmbH), and E. Reichert (Genisphere) for helpful discussions and for some of the figures. Furthermore, we are indebted to Prof. A. H. Soloway and Prof. R. F. Barth helpful discussions and valuable information material. H.F. and R.H. also thank the Fonds der Chemischen Industrie (FCI) for financial support. S.-E.S. thanks the Alexander von Humboldt foundation for a fellowship.

Received: June 25, 2001 [M 1522]

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New Methods for the High-Throughput Screening of Enantioselective Catalysts and Biocatalysts

Manfred T. Reetz*

The importance of asymmetric catalysis is undisputed, as evidenced, amongst other things, by the 2001 Nobel Prize for Chemistry to K. Barry Sharpless, Ryoji Noyori, and William S. Knowles. The two major options available to chemists are homogeneous transition metal catalysts^[1] and biocatalysts.^[2] In the former case ligand tuning based on intuition, knowledge of the reaction mechanism, molecular modeling as well as some degree of trial and error is the key to success.

In the 1990s a new technique emerged which has been loosely called combinatorial asymmetric catalysis.^[3] This involves time-saving parallel synthesis and the testing of large numbers of chiral catalysts. The challenges in this interesting new area of asymmetric catalysis are twofold, which center around strategies for the modular synthesis of chiral ligands and on developing high-throughput assays for determining the enantiomeric excess (*ee*).^[4] So far, the size of the catalyst libraries has usually been limited to less than a hundred or so catalysts, which were often analyzed conventionally.

The potential of combinatorial asymmetric catalysis has not been exploited to its full extent. Successfully finding hits is likely to increase upon expanding the size of the libraries. In the case of enzyme catalysis, the idea of applying the molecular biological methods of directed evolution in the creation of enantioselective enzyme mutants (variants) has been put into practice recently.^[5, 6] The underlying concept goes beyond combinatorial catalysis, since it is based on repeating rounds of mutagenesis/screening which create an evolutionary pressure without the need to know the structure or mechanism of the enzymes. The size of each library of mutant enzymes produced by error-prone polymerase chain reaction or DNA shuffling typically amounts to several thousand members, which poses a truly difficult analytical problem if each of them is to be tested for enantioselectivity in a given reaction.

It is clear that both approaches to asymmetric catalysis require the availability of high-throughput *ee* screening systems. The first *ee* assay designed to handle a reasonably large number of samples was a rather crude UV/Vis-based screen-

ing system for the lipase-catalyzed kinetic resolution of chiral *p*-nitrophenol esters. The *R* and the *S* esters were tested separately pairwise on a 96-well microtiter plate using a simple UV/Vis-based plate reader.^[5a] The concept of testing *R* and *S* substrates separately in kinetic resolution has some disadvantages.^[4] Nevertheless, it forms the basis of other tests as well,^[4] including an interesting recent development using coupled enzymatic transformations.^[7] Several more general screening systems have been devised, such as methods based on the mass spectrometric analysis of deuterium-labeled substrates that allow for 1000 *ee* determinations per day (which has now been extended to 10000 by using an eight-channel, multiplexed sprayer system),^[8] the use of capillary array electrophoresis (in some cases up to 30000 *ee* determinations per day),^[9] and the use of HPLC/circular dichroism (CD) spectroscopy (typically 1000 samples per day).^[10]

These and other methods were reviewed last year.^[4] Nevertheless, continued efforts in this fascinating area of research are necessary because no single assay is universal. van Delden and Feringa have recently reported an ingenious color test for enantioselectivity based on chirality-dependent color generation in doped films of liquid crystals.^[11] It remains to be seen if this interesting system can be modified into a high-throughput *ee* assay.

Recently, several new approaches to the high-throughput analysis of enantioselective catalysts have been described. A novel technique reported by Shair and co-workers makes use of DNA microarrays.^[12] This type of technology had previously been used to determine relative levels of gene expression on a genome-wide basis, as measured by the ratio of fluorescent reporters.^[13] In the newly developed *ee* assay, the goal was to measure the enantiopurity of chiral amino acids.^[12] One can imagine that such *R/S* mixtures could be produced by Rh-catalyzed hydrogenation of the corresponding *N*-acylamino acrylate by using a library of combinatorially prepared catalysts. In the model study, mixtures of an *R* and *S* amino acid were first subjected to acylation at the amino function to form *N*-Boc-protected derivatives (Boc = *tert*-butoxycarbonyl). Samples were then covalently attached to amine-functionalized glass slides in a spatially arrayed manner (Figure 1). In a second step the uncoupled surface amino functions were acylated exhaustively. The third step involved complete deprotection to afford the free amino function of the amino acid. Finally, in a fourth step two pseudo-enantiomeric

[*] Prof. Dr. M. T. Reetz
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2985
E-mail: reetz@mpi-muelheim.mpg.de

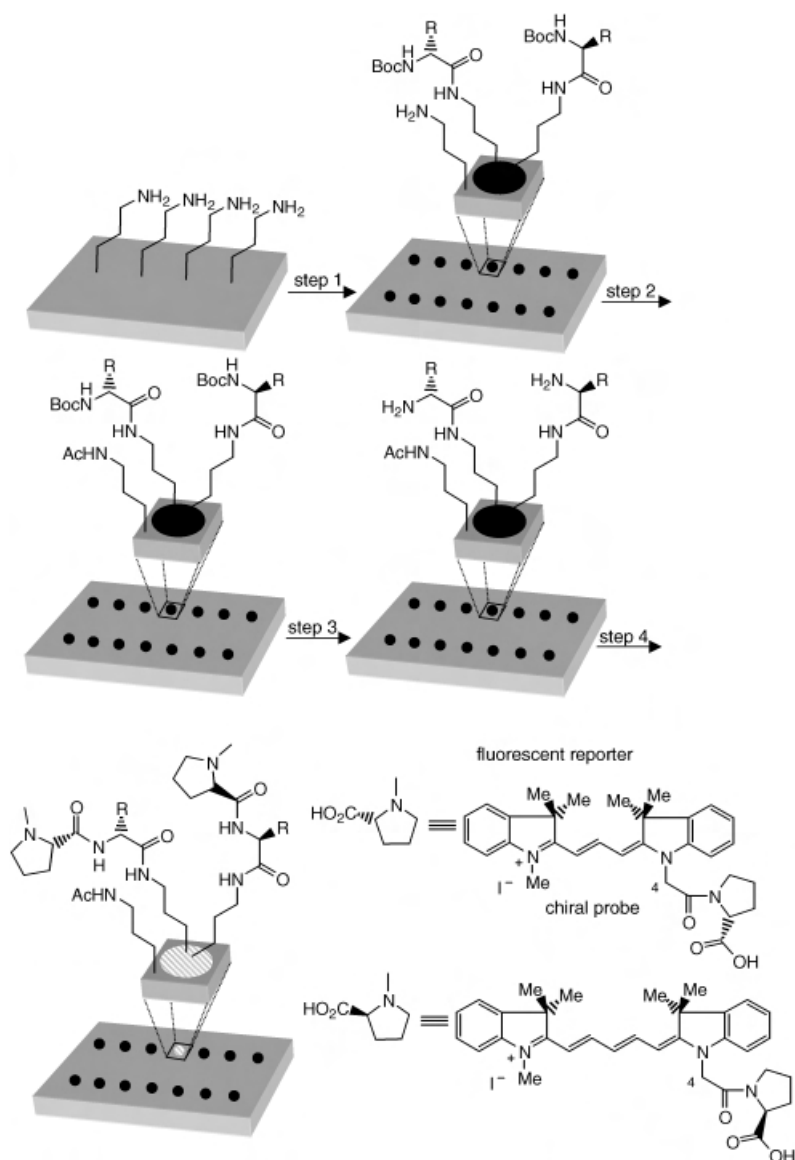


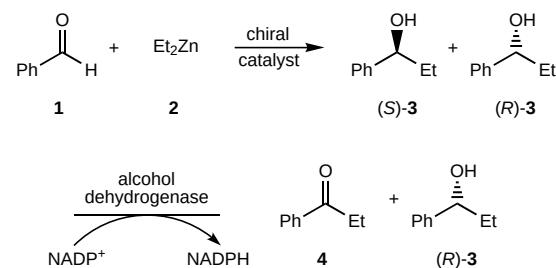
Figure 1. Reaction microarrays in high-throughput *ee* determination. Reagents and conditions:^[12] step 1) BocHNCH(R)CO₂H, PyAOP, *i*Pr₂NEt, DMF; step 2) Ac₂O, pyridine; step 3) 10% CF₃CO₂H and 10% Et₃SiH in CH₂Cl₂, then 3% Et₃N in CH₂Cl₂; step 4) pentafluorophenyl diphenylphosphinate, *i*Pr₂NEt, 1:1 mixture of the two fluorescent proline derivatives, DMF, -20 °C. PyAOP = 7-azabenzotriazol-1-yloxytris(pyrrolidino) phosphonium hexafluorophosphate.

fluorescent probes were attached to the free amino groups on the surface of the array.

An appreciable degree of parallel kinetic resolution in the process of amide coupling is a requirement for the success of the *ee* assay,^[12] which is similar to a mass spectrometric based system previously devised by Finn and co-workers.^[14] In the present case the *ee* values are accessible by measuring the ratio of the relevant fluorescent intensities. It was reported that 8000 *ee* determinations are possible per day, with precision amounting to $\pm 10\%$ of the actual value. It remains to be seen whether DNA microarray technology can be modified in an analogous manner in the case of other types of substrates.^[19]

Abato and Seto have described an enzymatic method for determining enantiomeric excess (EMD_{ee}).^[15] The method is

based on the idea that an appropriate enzyme can be used to selectively process one enantiomer of a product from a catalytic reaction. The well-known catalytic addition of diethylzinc (**2**) to benzaldehyde (**1**) was chosen as a test-bed for demonstrating EMD_{ee}. The reaction product, 1-phenylpropanol (**3**), can be oxidized to ethyl phenyl ketone (**4**) using the alcohol dehydrogenase from *Thermoanaerobium* sp., this process being completely *S* selective (Scheme 1). It was possible to measure the rate of this enzymatic oxidation by monitoring the formation of NADPH by UV spectroscopy at 340 nm.



Scheme 1. EMD_{ee} in the case of 1-phenylpropanol produced by asymmetric addition of diethylzinc to benzaldehyde.^[15]

Decisive for the success of the assay is the finding that the rate of oxidation constitutes a direct measure of the *ee* value (Figure 2).^[15] High-throughput was demonstrated by analyzing 100 samples in a 384-well format by using a UV/fluorescence plate reader. Each sample contained 1 μ mol of 1-phenylpropanol (**3**) in a volume of 100 μ L. The accuracy of the *ee* value amounts to $\pm 10\%$, as checked by independent GC determinations. About 100 samples can be processed in 30 minutes,^[15] which calculates as 4800 *ee* determinations per day.

As noted by the author, EMD_{ee} does not distinguish between processes that proceed with low enantioselectivity but high conversion and high enantioselectivity but low conversion. EMD_{ee} was

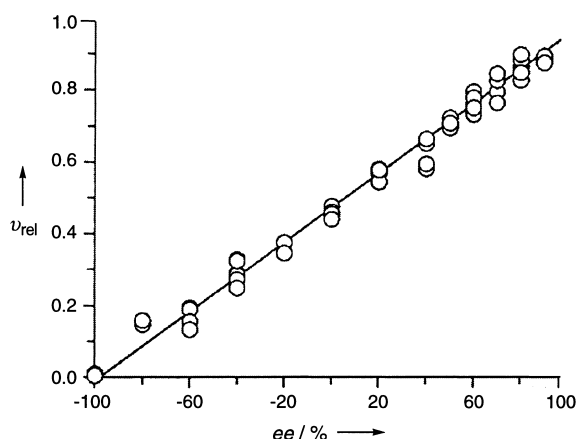
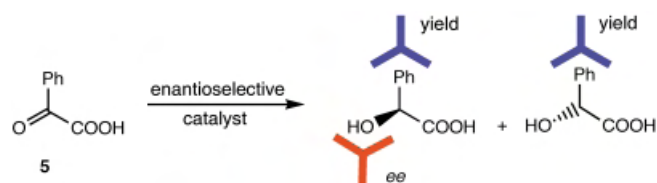


Figure 2. Plot of the initial rate of the enzyme-catalyzed oxidation of 1-phenylpropanol as a function of the *ee* value (the solid line represents a fit of the data to the Michaelis–Menten formalism for competitive inhibition where $[S] = [(S)\text{-}3]$ and $[I] = [(R)\text{-}3]$).^[15] The total alcohol concentration was maintained constant at 10 mM.

therefore extended to provide information regarding both the *ee* value and conversion.^[15] Accordingly, in a second set of assays the *R*-selective alcohol dehydrogenase from *Lactobacillus kefir* was used to quantify the amount of (*R*)-**3** present in the mixture. The conversion can be calculated since the amounts of (*R*)-**3** and (*S*)-**3** are known.

The question arises as to the generality of the EMDee assay in the case of other chiral alcohols which do not show such high enantioselectivity in the oxidation catalyzed by alcohol dehydrogenase. Theoretically, the test should still work, although accuracy in such cases would have to be demonstrated. It may be easier to use a different, more selective alcohol dehydrogenase, and indeed a large number of such enzymes are commercially available. In summary, EMDee constitutes an interesting way to determine the *ee* value of alcohols in a high-throughput manner by using standard instrumentation. Of course, the assay has to be optimized for each new chiral alcohol under study.

A third recent development, reported by Wagner, Mioskowski, and co-workers, concerns high-throughput screening of enantioselective catalysts by enzyme immunoassays,^[16] a technology that is routinely applied in biology and medicine. The new assay was illustrated by analyzing *R/S* mixtures of mandelic acid prepared by the enantioselective Ru-catalyzed hydrogenation of benzoyl formic acid (**5**; Scheme 2). By employing an antibody that binds both enantiomers it was possible to measure the concentration of the reaction product, thereby allowing the yield to be calculated. The use of an *S*-specific antibody then makes the determination of the *ee* value possible.



Scheme 2. High-throughput screening of enantioselective catalysts by competitive enzyme immunoassays.^[16] The antibody marked blue recognizes both enantiomers, whereas the antibody marked red is *S* specific, thus making the determination of yield and *ee* value possible.

Although this procedure may sound complicated to some organic chemists, and in fact details need to be consulted, antibodies can be raised to almost any compound of interest. Moreover, simple automated equipment comprising a plate washer and plate absorbance reader is all that is necessary. About 1000 *ee* determinations are possible per day, with precision amounting to $\pm 9\%$.^[16]

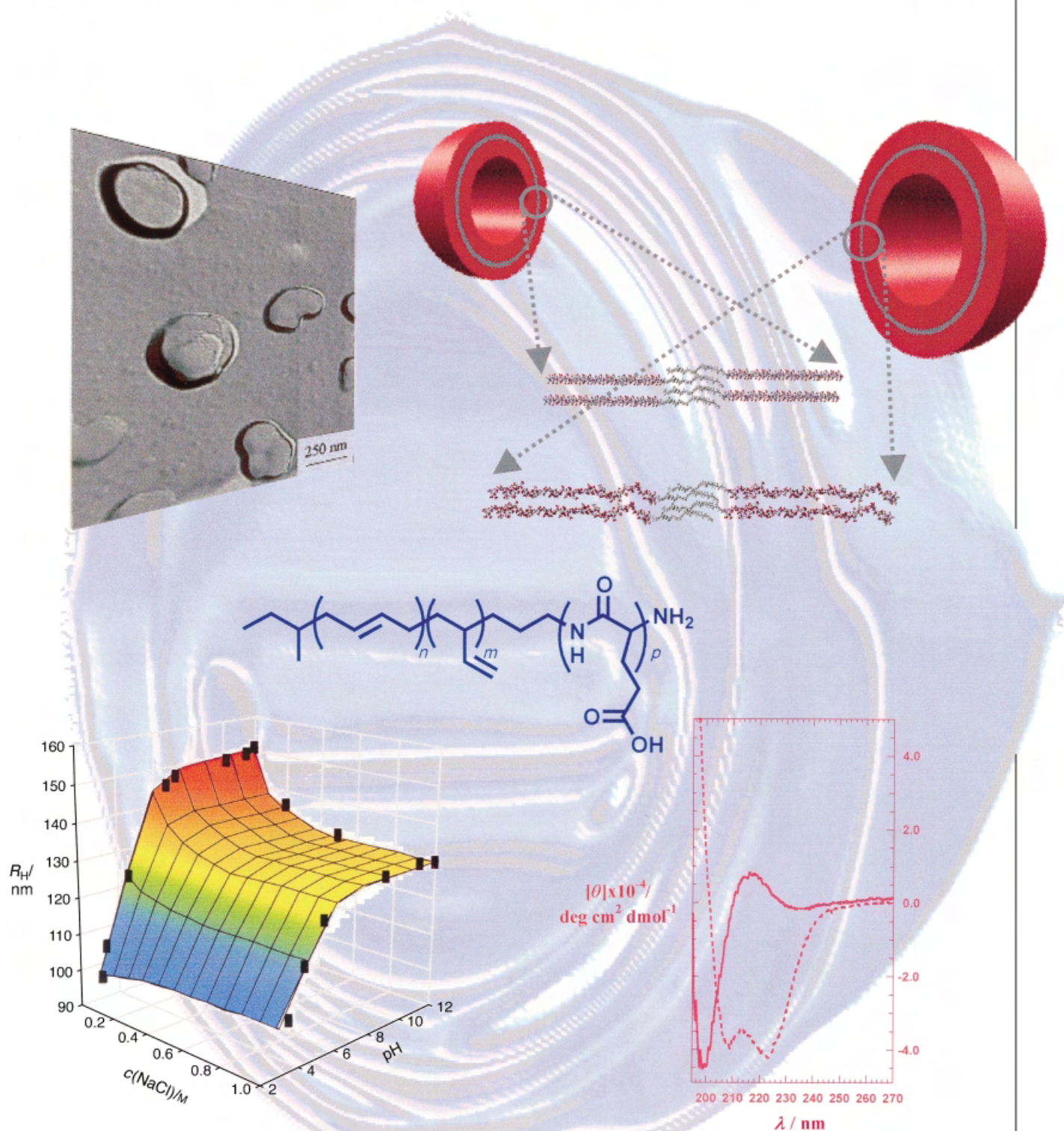
In summary, several novel high-throughput *ee* assays have been reported recently,^[7, 12, 15, 16] thus extending the list of previously developed systems.^[4] Yet another *ee* assay has been devised in the author's laboratories which utilizes NMR detection, and makes possible at least 1000 *ee* determinations per day with surprisingly high accuracy.^[17] Perhaps one of the advantages of this system has to do with the fact that organic chemists are well acquainted with NMR spectroscopy. The decision as to which *ee* screening system to use also depends upon the particular analytical problem. If medium-through-

put is sufficient for a given purpose, that is, 300–700 samples per day, even classical gas or liquid chromatography in properly modified forms may suffice. Such a system comprising two GC columns in separate ovens, a single prep-and-load sample manager, and one PC has been shown to function well for certain substrates (500–700 *ee* determinations per day).^[18] The precision of the *ee* determination is another criterion which needs to be considered, and depends upon the particular analytical problem. Screening for hits in combinatorial asymmetric transition metal catalysis or in the early phases of directed evolution of an enantioselective enzyme may not require maximum precision in the *ee* value. However, in the late stages of a directed evolution project, for example, when attempting to increase the *ee* value in a stepwise manner from typically 90% to higher values, high analytical precision does in fact become important.

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Self-assembly of a peptide-based diblock copolymer has been used to create new shape-persistent stimuli-responsive nanoparticles in water which are like vesicles.



For more information
see the following pages.

Water-Soluble Stimuli-Responsive Vesicles from Peptide-Based Diblock Copolymers**

Frédéric Chécot, Sébastien Lecommandoux,*
Yves Gnanou, and Harm-Anton Klok*

Over the past few years increasing attention has been paid to the supramolecular organization of water-soluble block copolymer surfactants and to their potential use in applications such as coatings, drug delivery systems, nanoparticles, and nanoreactors.^[1–3] An important issue in making these self-assembled systems useful for specific applications is their capability to respond to external stimuli such as temperature and/or pH.^[4] Very recently, Jérôme and co-workers reported the formation in water of three-layer micelles from a polystyrene-*b*-poly(2-vinylpyridine)-*b*-poly(ethylene oxide) (PS-*b*-P2VP-*b*-PEO) triblock copolymer.^[5] These authors demonstrated that the pH sensitivity of the P2VP shell can be used to tune the micelle size from a hydrodynamic diameter (D_H) of 75.4 nm at pH > 5 to 135.2 nm at pH < 5. This effect is based on the electrostatic repulsion between the charged P2VP blocks and is not completely reversible because of the formation of salt with each pH cycle.^[5] Another important issue in the design of a self-assembled material is its stability. In fact, most aggregates are only stable within a certain range of concentration, temperature, or pH values. A suitable approach to improve the stability of self-assembled structures is to cross-link one of their blocks.^[6]

We report here on the self-organization of a polybutadiene-*b*-poly(L-glutamic acid) (PB-*b*-PGA) diblock copolymer in aqueous solution. Our aim is to exploit the pH sensitivity of the secondary structure of polypeptides to manipulate the size and shape of the supramolecular structures formed by self-assembly of these block copolymers in aqueous medium. In addition to providing the hydrophobic driving forces for the self-assembly, the polybutadiene block may also allow the supramolecular structure to be captured indefinitely by UV-induced cross-linking of its 1,2-vinyl bonds, and thus provide access to novel “shape-persistent stimuli-responsive nanoparticles”. Stimuli-responsive nanoparticles have been reported before, and typically rely on changes in the swelling behavior induced by changes in pH value, ionic strength, or solvent quality.^[4] The use of polypeptide-based diblock copolymers for the preparation of such structures, however,

is unprecedented. In contrast to most other amphiphilic polyelectrolyte (block) copolymers, the hydrophilic peptide block has the ability to fold into a well-defined α -helical secondary structure. More importantly, the swelling behavior of nanoparticles composed of peptide-based block copolymers may be regulated by changes in the pH or ionic strength which induce changes in the conformation of the peptide block; these changes can be precisely controlled by appropriate design of the amino acid sequence.

The diblock copolymer was prepared as shown in Scheme 1. The first step involved the ring-opening polymerization of γ -benzyl-L-glutamate *N*-carboxyanhydride (Bn-GluNCA) using an ω -aminopolybutadiene as an initiator followed by a hydrogenation step to remove the benzyl ester protecting groups. The number average degree of polymerization of the polybutadiene block is about 40 and about 100 for the poly(L-glutamic acid) one. The PB₄₀-*b*-PGA₁₀₀ copolymer readily dissolved in water upon addition of one equivalent of NaOH. In a first series of experiments, the critical aggregation concentration (cac) of the block copolymer was determined by using pyrene as a fluorescent probe.^[7] Solutions of PB₄₀-*b*-PGA₁₀₀ with concentrations ranging from 10^{−7} to 10^{−5} M were prepared with a constant pyrene concentration of 6.10^{−7} M. Both the excitation and emission spectra were recorded. A red-shift of the pyrene (0,0) band from 335.5 to 339 nm was observed on increasing the copolymer concentration (Figure 1). This change reflects the transfer of pyrene from water into the hydrophobic part of the supramolecular aggregate. A plot of the ratio of the intensity of the signal at 339 nm to that at 335.5 nm ($I_{339}/I_{335.5}$) versus the block copolymer concentration (Figure 1) resulted in a cac value of about 10^{−6} M, a value typical for amphiphilic block copolymers.^[3]

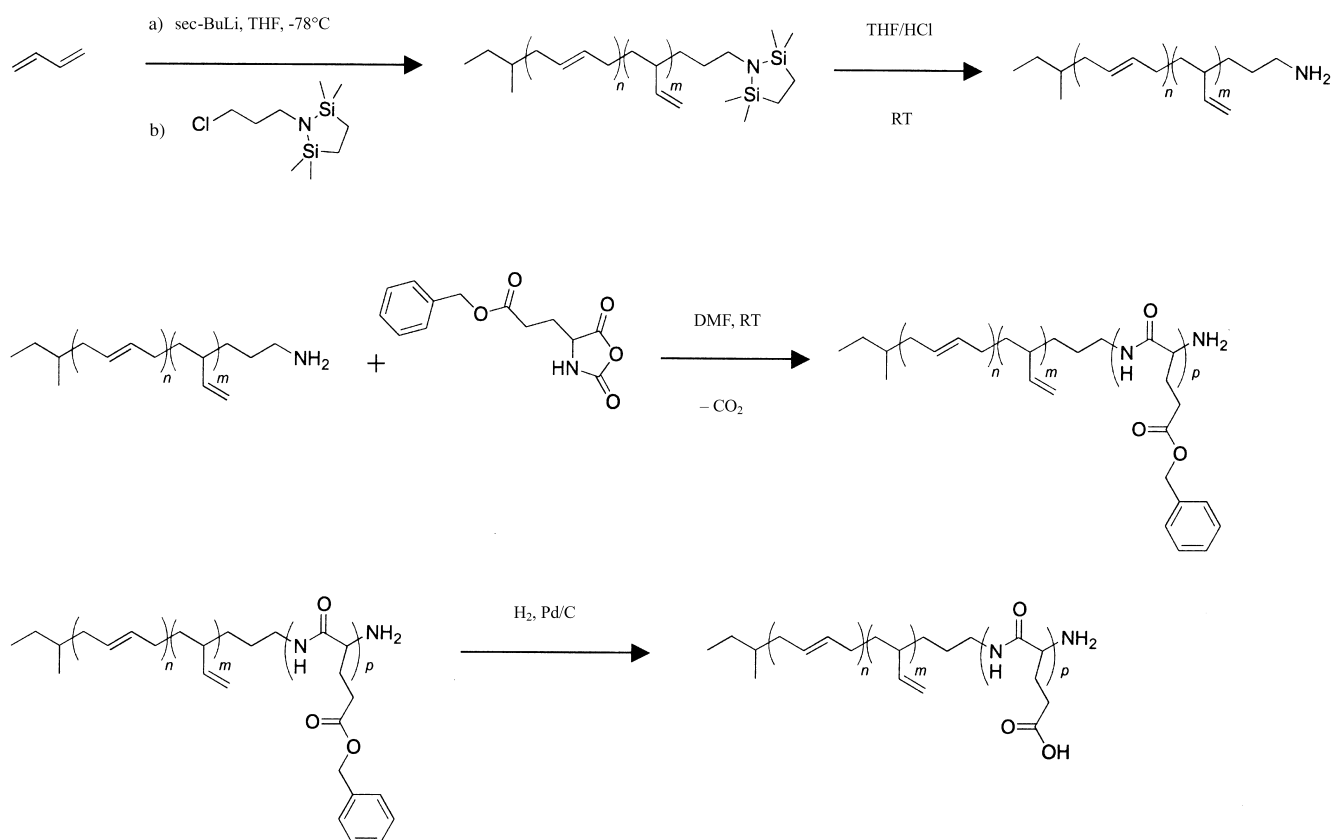
The supramolecular organization of the PB₄₀-*b*-PGA₁₀₀ block copolymer in aqueous solutions at pH 11 was investigated by means of dynamic light scattering (DLS) studies. These experiments were carried out with block copolymer concentrations ranging from 0.31 to 2 g L^{−1}, both with and without added salt (NaCl), and covered a wide range of angles (from 40 to 140°). The analysis of the autocorrelation functions $C(q,t)$, where q is the scattering vector and t the time, was carried out following the cumulants method (Figure 2).^[8] The CONTIN analysis of the same autocorrelation functions showed only one peak,^[9] thus confirming the formation of only one population of particles with a very low size polydispersity index (PDI) of 0.04 (± 0.007). A time-dependent study of the hydrodynamic radius of the aggregates at an angle of 90° indicated that a perfect equilibrium state was reached after about ten days of vigorous stirring. The hydrodynamic radius (R_H) of the corresponding equilibrated aggregates was determined by extrapolating $R_H(c)$ to $c \rightarrow 0$ to be approximately 128 nm in the absence of salt and about 114 nm in the presence of 1 M NaCl. This decrease in the particle size reflects the screening of the electrostatic charges upon addition of salt.

In addition to DLS studies, static light scattering experiments (SLS) were performed in water under the same conditions ($0.31 \leq c \leq 2$ g L^{−1}, $40 \leq \theta \leq 140^\circ$) with added salt (1 M NaCl). A radius of gyration (R_g) of 110 nm was obtained from these studies.^[10] The ratio R_g/R_H (where R_H was

[*] Dr. S. Lecommandoux, F. Chécot, Dr. Y. Gnanou
Laboratoire de Chimie des Polymères Organiques
École Nationale Supérieure de Chimie et Physique de Bordeaux
Université Bordeaux 1
16 Avenue Pey-Berland, 33607 Pessac (France)
Fax: (+33) 5-56-84-84-87
E-mail: s.lecommandoux@enscpb.u-bordeaux.fr

Dr. H.-A. Klok
Max-Planck-Institute for Polymer Research
Ackermannweg 10, 55128 Mainz (Germany)
Fax: (+49) 6131-379-100
E-mail: hak@mpip-mainz.mpg.de

[**] Financial support by the CNRS, MENRT, DAAD, Fonds der Chemischen Industrie, and the Deutsche Forschungsgemeinschaft (Emmy Noether Programm, KL1049/2) is gratefully acknowledged. S.L. and H.-A.K. are grateful to Dr. R. Borsali and Prof. K. Müllen, respectively, for their interest and support.



Scheme 1. Reaction scheme for the synthesis of the PB₄₀-b-PGA₁₀₀ diblock copolymer by combination of anionic and *N*-carboxyanhydride ring-opening polymerizations.

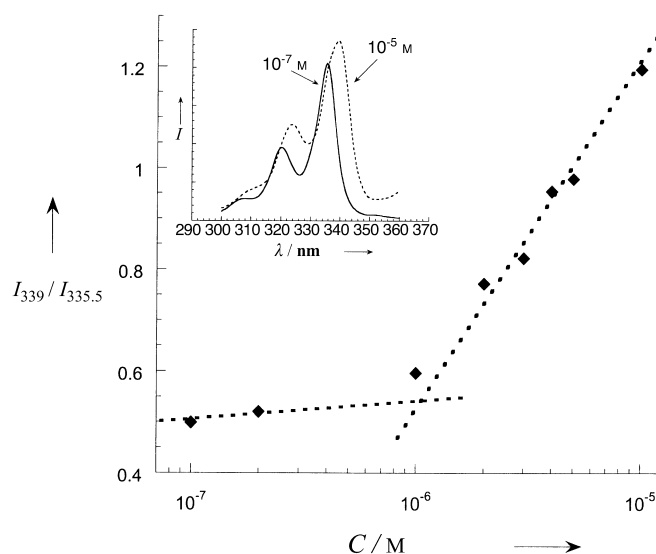


Figure 1. Intensity ratio $I_{339}/I_{335.5}$ obtained from the fluorescence excitation spectra of pyrene plotted versus PB₄₀-b-PGA₁₀₀ concentration. Inset: fluorescence excitation spectra of pyrene (6.10^{-7} mol L⁻¹) below (—) and above (---) the cac.

determined in the same conditions (114 nm)) is 0.97/1, which is different from the expected theoretical values for a uniform sphere (0.774/1) or a polymer coil (1.50/1), but is very close to that expected (1.0/1) for a hollow sphere, which suggests there is a vesicle-type morphology.^[11] Comparison of the average extended length of a PB₄₀-b-PGA₁₀₀ molecule (approximately

25 nm under these conditions) with the measured radii (about 120 nm) also suggests that a vesicle-type morphology (Figure 3) is more likely than a micellar structure. These arguments are supported by freeze-fracture transmission electron microscopy (TEM) experiments (Figure 4). The PB₄₀-b-PGA₁₀₀ sample ($c = 1.25$ g L⁻¹) was dissolved in a water/glycerol solvent mixture (7/3) to avoid water crystallization.^[12] Aggregates with apparent radii $R_{\text{TEM}} \approx 120$ nm were observed by this technique, which are in agreement with the results obtained by DLS and SLS experiments.

Next, the effects of pH changes on the secondary structure of the peptide block of the aggregates were investigated by circular dichroism (CD). The CD spectra recorded in aqueous solution at pH 4.5 and pH 11.5 are shown in Figure 5. The spectrum obtained at pH 4.5, with negative minima at 221 and 208 nm and a positive maximum at 190 nm, is typical of an α -helical secondary structure.^[13] PB₄₀-b-PGA₁₀₀ gives a doubly inflected CD curve at pH 11.5 with a small positive maximum at 218 nm and a large minimum at 197 nm, which indicates there is a random coil conformation. The observed pH-dependence of the secondary structure of the PGA block of the aggregates is identical to the behavior known for poly(L-glutamic acid) homopolymers.^[13]

The effect of pH-induced changes of the polypeptide secondary structure on the size of the aggregates was investigated by DLS studies. Figure 6 shows the R_{H} value as a function of both the pH value and NaCl concentration. These data illustrate that even at high NaCl concentrations,

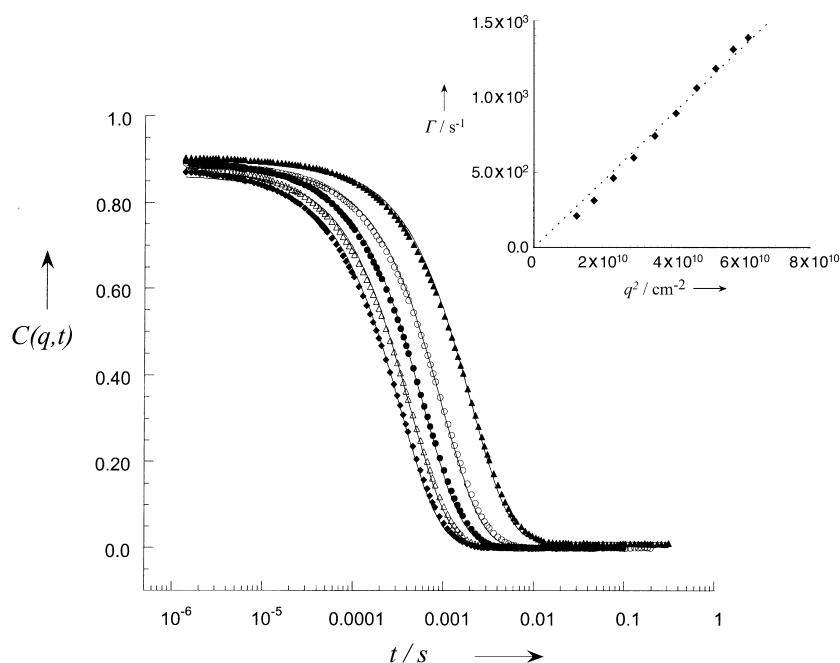


Figure 2. Autocorrelation functions of $PB_{40}\text{-}b\text{-}PGA_{100}$ vesicles in water ($c = 0.625 \text{ g L}^{-1}$) at different scattering angles: $\blacktriangle$: 50° ; $\circ$: 70° ; $\bullet$: 90° ; $\triangle$: 110° ; $\blacklozenge$: 130° . The lines represent data fits with a mono-exponential decay function. Inset: Dependence of the first cumulant frequency (Γ) on the square of the scattering vector (q^2).

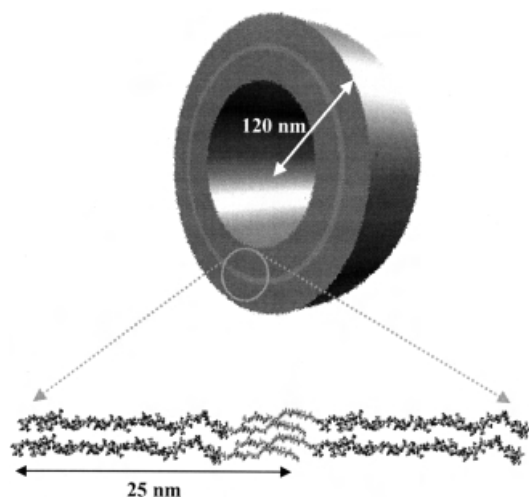


Figure 3. Proposed model for the self-assembly of the $PB_{40}\text{-}b\text{-}PGA_{100}$ into vesicular aggregates.

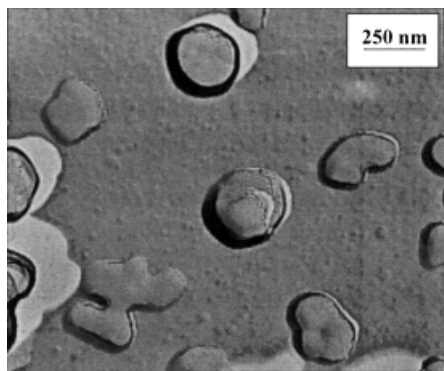


Figure 4. Freeze-fracture TEM image of the $PB_{40}\text{-}b\text{-}PGA_{100}$ aggregates obtained from a water/glycerol (7/3) mixture.

when charges on the polypeptide block are completely screened, the size of the aggregates can still be varied by changing the pH value. These pH-induced changes in size (as evidenced from the CD spectra in Figure 5) correlate with a transition from a compact α -helical secondary structure at low pH values to a more extended random-coil conformation in basic media. Such pH-induced size variations are completely reversible and can be repeated numerous times.

In summary, the $PB_{40}\text{-}b\text{-}PGA_{100}$ diblock copolymer forms well-defined vesicular morphologies after direct dissolution into water (basic pH).^[14] Dissolution by dialysis and under different pH conditions might certainly lead to other morphologies: this aspect is currently under investigation.^[15] The size of the aggregate can be manipulated reversibly by changing the pH value and ionic strength. Even at high NaCl concentrations, where all the charges are effectively screened, pH-induced changes in the polypeptide secondary structure can be used to reversibly vary the aggregate dimensions. Compared with

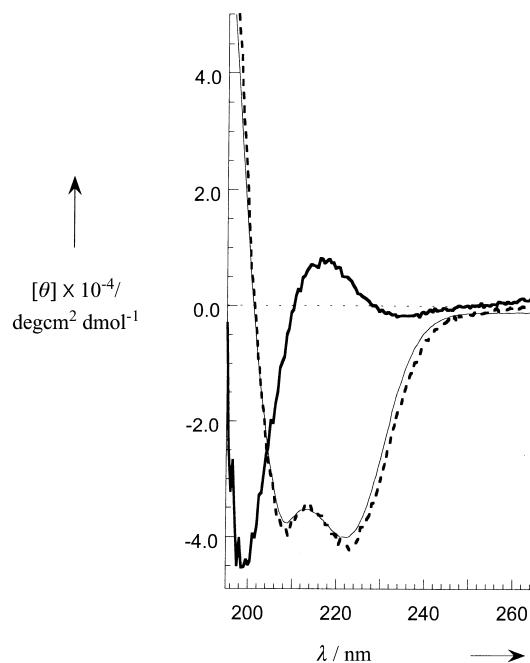


Figure 5. CD spectra of $PB_{40}\text{-}b\text{-}PGA_{100}$ as a function of pH: —: pH 11.5 (coil conformation), ---: pH 4.5 (α -helical conformation). —: CD spectrum obtained for a poly(L-glutamic acid) homopolymer with a molecular weight of 32 kDa at pH 4.5.

other polyelectrolyte-based block copolymers, this $PB_{40}\text{-}b\text{-}PGA_{100}$ diblock copolymer possesses the unique feature that the polypeptide block is capable of folding into a compact and well-defined secondary structure. It is possible to covalently “capture” the morphology of the system and transform a transient supramolecular self-assembled aggregate into a permanent shape-persistent stimuli-responsive nanoparticle

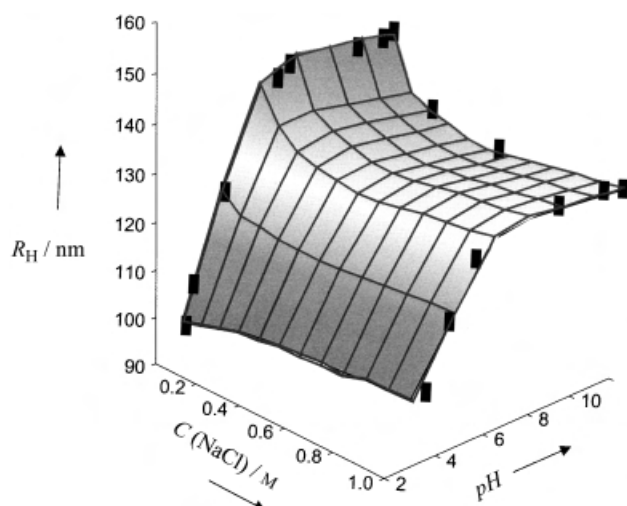


Figure 6. Hydrodynamic radius (R_H) of PB_{40} - b - PGA_{100} vesicles measured by DLS studies as a function of ionic strength (NaCl salt concentration) and pH value. ■: experimental data.

by using the 1,2-vinyl bonds present in the polybutadiene. First experiments have shown a moderate shrinkage of the vesicle size after UV curing, which is a typical phenomenon accompanying the cross-linking of polybutadiene molecules. Such nanoparticles might be suitable for a number of applications including the encapsulation and/or the release of hydrophilic as well as hydrophobic active species or their use as sensor nanodevices.

Experimental Section

PB_{40} - b - PGA_{100} : Anionic polymerization of butadiene in THF at -78°C using sec-butyllithium as initiator followed by quenching the oligobutadienyllithium with 1-(3-chloropropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane and acidic aqueous workup gave the ω -amino oligobutadiene. The oligomer functionalized at the primary amine end was then used to initiate the ring-opening oligomerization of Bn-GluNCA in DMF.^[16] The length of the γ -benzyl-L-glutamate segment could be controlled through the molar ratio of Bn-GluNCA to ω -amino oligobutadiene initiator to give the required polybutadiene- b -poly(γ -benzyl-L-glutamate) block copolymer. After removal of the benzyl ester groups by hydrogenation, the amphiphilic diblock copolymer PB_{40} - b - PGA_{100} was obtained. The composition of the block copolymer was analyzed by means of ^1H and ^{13}C NMR spectroscopy and gel permeation chromatography.

SLS and DLS measurements were performed on a ALV5000 goniometer equipped with a ALV5000/E Multiple Tau digital Realtime correlator. The R_H and PDI values of the aggregates were obtained by a cumulant and CONTIN analysis of the experimental correlation functions. TEM pictures were recorded on a JEOL JEM100S microscope working at 80 KV. Samples were prepared by freeze–fracture process on 1.25 g L^{-1} copolymer solutions (7/3 water/glycerol). Fluorescence spectra were recorded on a SAFAS Spectrofluorometer flx spectrometer. CD experiments were carried out on a JOBIN YVON CD6 Spex spectrometer (184–900 nm).

Received: December 21, 2001 [Z18426]

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Dual Biosensing by Magneto-Controlled Bioelectrocatalysis**

Eugenii Katz, Laila Sheeney-Haj-Ichia,
Andreas F. Bückmann, and Itamar Willner*

In the last two decades extensive research efforts were directed towards the development of amperometric biosensors based on redox-active enzymes.^[1, 2] Ingenious methods to electrically contact redox enzymes with electrode supports by tethering relay units to the protein,^[3] the immobilization of

[*] Prof. I. Willner, Dr. E. Katz, L. Sheeney-Haj-Ichia
Institute of Chemistry
The Hebrew University of Jerusalem
Jerusalem 91904 (Israel)
Fax: (+972) 2-6527715
E-mail: willnea@vms.huji.ac.il
A. F. Bückmann^[†]
Department of Molecular Structure Research
Gesellschaft für Biotechnologische Forschung
Mascheroder Weg 1, 38124 Braunschweig (Germany)

[**] This research is supported by the German–Israel Project Cooperation (DIP). I.W. acknowledges the Max Planck Award for International Cooperation.

[†] Deceased, October 2001

the biocatalysts in redox polymers,^[4] or the reconstitution of the enzymes with relay-cofactor units,^[5] were developed. The development of multifunctional electrodes that allow the simultaneous analysis of two (or more) substrates remains, however, a challenging subject in bioelectronics. The use of a photoswitchable enzyme as a biocatalytic component in a two-enzyme bifunctional sensor system was suggested as a means to analyze two different substrates by an integrated biosensor.^[6] That is, in the photochemically switched “off” state of the enzyme, the amperometric response corresponding to the analysis of one of the substrates is recorded, whereas in the photochemically switched “on” state of the second enzyme the cumulative amperometric response, which corresponds to the analysis of the sum of the substrates is recorded. Thus, by a two-step detection procedure, the two substrates can be analyzed quantitatively. Besides the complexity of this concept, the phototriggered redox enzymes cannot be fully switched off and on, and therefore a different methodology to resolve this basic goal is required. Recently we reported the magnetic control of bioelectrocatalyzed transformations by the application of redox-relay-functionalized magnetite particles, and an external magnetic field as a triggering signal.^[7] In contrast to extensive research efforts that utilize magnetic particles for the separation or concentration of molecular or biomolecular components,^[8, 9] our approach of tethering redox-active units to magnetic particles, and the accompanying magnetically controlled electrochemical activation of chemical transformations, is a novel concept in electrocatalysis,^[10] and bioelectrocatalysis.^[7] Here we report

the dual analysis of two substrates by the application of two enzymes, a relay-monolayer-functionalized electrode, relay-NAD⁺-cofactor-functionalized magnetic particles, and the use of an external magnetic field.

Pyrroloquinoline quinone (PQQ; **1**), acts as an electrocatalyst for the oxidation of reduced 1,4-dihydronicotinamide adenine dinucleotide (NADH).^[11] Accordingly, aminopropyl-siloxane-functionalized magnetic particles were modified with **1**. Aminoethyl-functionalized-NAD⁺ (aNAD⁺; **2**)^[12] was coupled to the PQQ-modified magnetic particles. By coulometric analysis of the redox-wave of PQQ in the cyclic voltammogram of the aNAD⁺-PQQ-functionalized magnetic particles, and knowing the size of the particles, we estimated the surface coverage to be around 1000–3000 PQQ units per particle. Earlier we demonstrated that the PQQ/aNAD⁺ ratio in the assembly is approximately 1.^[13] A cystamine-functionalized Au-electrode was modified with *N*-(ferrocenylmethyl)amino-hexanoic acid (Fc; **3**).^[14] Coulometric analysis of the redox wave of the Fc units indicates a surface coverage corresponding to about 5×10^{-11} mol cm⁻².

The analysis system (Figure 1) consists of the Fc-modified Au-surface as a working electrode, the aNAD⁺-PQQ-functionalized magnetic particles, the two enzymes, glucose oxidase (GOx; E.C.1.1.3.4 from *Aspergillus niger*), and lactate dehydrogenase (LDH; E.C.1.1.1.27 from rabbit muscle, type II), and the two substrates, glucose and lactic acid. Figure 2A shows the cyclic voltammogram observed for the system that lacks the two substrates, with the external magnet positioned above the electrochemical cell. Only the redox

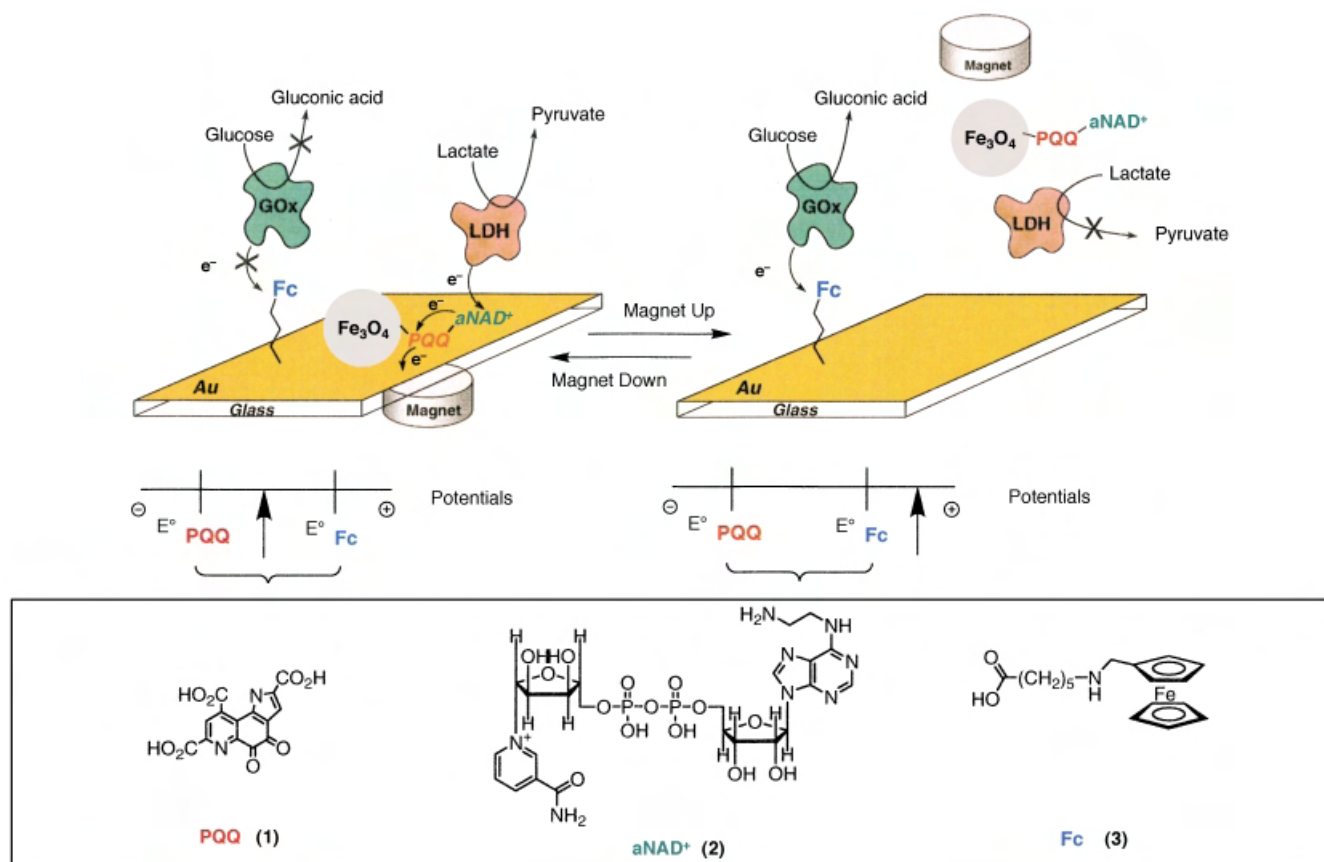


Figure 1. Magneto-switched dual biosensing of glucose and lactate.

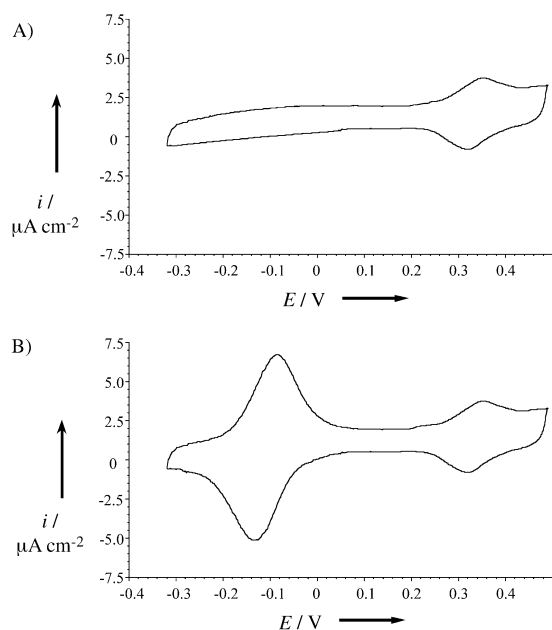


Figure 2. A) Cyclic voltammogram of the Fc-monolayer-functionalized Au electrode when the aNAD⁺-PQQ-functionalized magnetic particles are retracted from the electrode by the external magnet. B) Cyclic voltammogram of the Fc-monolayer-functionalized Au electrode in the presence of the aNAD⁺-PQQ-functionalized magnetic particles attracted to the electrode by the magnet. The data were recorded under argon in the presence of the magnetic particles, 20 mg, in 0.1 M Tris-HCl buffer, pH 7.0, CaCl₂, 10 mM. Potential scan rate, 100 mV s⁻¹.

process of the Fc monolayer is observed, $E^\circ = 0.32$ V. Switching the magnet to a position below the working electrode attracts the magnetic particles to the surface, which results in the generation of the characteristic redox wave of the PQQ units, $E^\circ = -0.13$ V (pH 7.0), and the redox wave of the Fc monolayer associated with the electrode ($E^\circ = 0.32$ V, Figure 2B). By cyclic positioning of the external magnet above the electrochemical cell or below the electrode, the functionalized magnetic particles may be reversibly drawn away from the electrode or attracted to the electrode, respectively. The electrical response of the system is then cycled between the single redox wave of the Fc-monolayer-functionalized electrode, and the two redox waves corresponding to the aNAD⁺-PQQ-modified magnetic particles and the Fc-monolayer, respectively. The cyclic voltammograms shown in Figure 2 clearly reveal two potential regions where the detection of lactate or glucose may

be exploited. When the magnet is positioned above the electrode and only the Fc units immobilized at the electrode are electrochemically active, the ferrocene-mediated biocatalytic oxidation of glucose can be achieved at potentials more positive than 0.32 V. When the magnet is positioned below the electrode and the aNAD⁺-PQQ-functionalized magnetic particles are attracted to the electrode, the PQQ-mediated biocatalytic oxidation of lactate can be achieved in the potential region -0.13 V $< E < 0.32$ V. It should be noted that when the magnet is positioned below the electrode the two bioelectrocatalytic processes, oxidation of glucose and of lactate, will occur at the potentials more positive than 0.32 V, where both electron mediators, PQQ and ferrocene, are oxidized.

Figure 3A, curve b, shows the cyclic voltammogram observed in the system consisting of the functionalized particles, GOx and LDH, and the two substrates, lactate and glucose, in the potential range -0.1 V $- +0.6$ V, when the magnet is positioned above the cell. An electrocatalytic current corresponding to the Fc-mediated bioelectrocatalyzed oxidation of glucose by GOx is observed. Figure 3A, top (curve 1), shows the calibration curve corresponding to the amperometric responses of the system at variable concentrations of glucose. In this configuration the system is not sensitive to lactate in the entire concentration-range of glucose analysis, Figure 3A, top (curve 2). Figure 3B, curve b, shows the voltammetric

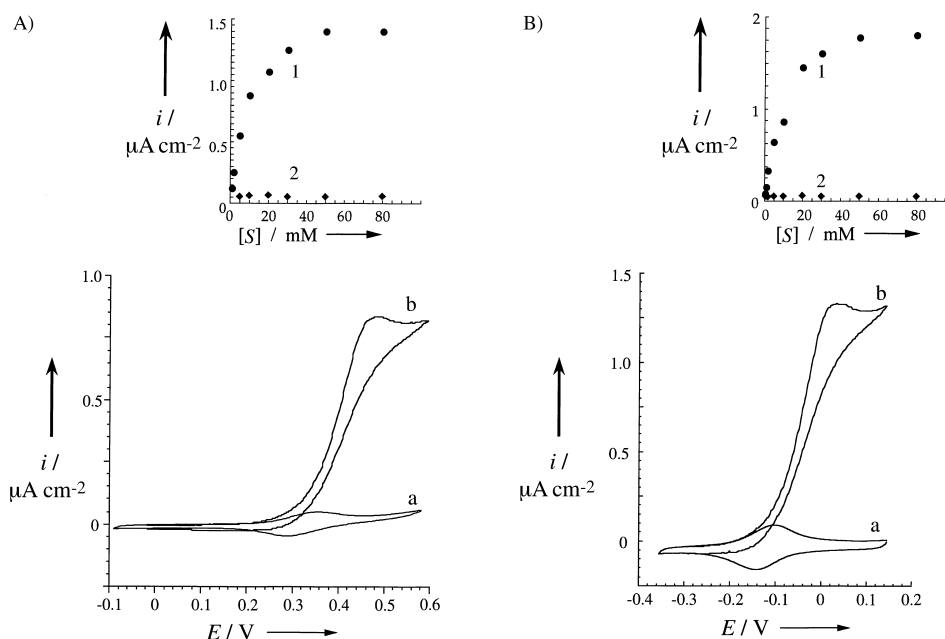


Figure 3. A) Bottom: cyclic voltammograms of the Fc-monolayer-functionalized Au electrode when the aNAD⁺-PQQ-functionalized magnetic particles are retracted from the electrode by the external magnet: a) in the presence of GOx, 1 mg mL⁻¹, LDH, 2 mg mL⁻¹; b) in the presence of GOx, 1 mg mL⁻¹, LDH, 2 mg mL⁻¹, glucose, 50 mM, lactate, 20 mM. Top: Calibration plot of the amperometric response of the system with the magnet in the "up" position and the applied potential $E = 0.50$ V: 1) at different concentrations of glucose; 2) at different concentrations of lactate; B) bottom: cyclic voltammograms of the Fc-monolayer-functionalized Au electrode in the presence of the aNAD⁺-PQQ-functionalized magnetic particles attracted to the electrode by the magnet: a) in the presence of GOx, 1 mg mL⁻¹, LDH, 2 mg mL⁻¹; b) in the presence of GOx, 1 mg mL⁻¹, LDH, 2 mg mL⁻¹, glucose, 50 mM, lactate, 20 mM. Top: Calibration plot of the amperometric responses of the system with the magnet in the "down" position and the applied potential $E = 0.05$ V: 1) at different concentrations of lactate; 2) at different concentrations of glucose. The data were recorded under argon in the presence of the magnetic particles (20 mg) in 0.1 M Tris-HCl buffer, pH 7.0, CaCl₂, 10 mM. Potential scan rate, 5 mV s⁻¹.

response of the same system upon shifting the magnet to below the electrochemical cell and recording the electrochemical response of the system in the potential range $-0.36\text{ V} - +0.15\text{ V}$. An electrocatalytic anodic current is observed at the potentials where PQQ is oxidized. Lactate reduces the NAD^+ -cofactor associated with the magnetic particles to NADH in the presence of LDH. The NADH is oxidized by PQQ which results in the formation of PQQH_2 and the regeneration of NAD^+ . The magnetic particles attracted to the electrode by the external magnet actuate the electrochemical oxidation of PQQH_2 , which results in the formation of the electrocatalytic anodic current. Figure 3B, top (curve 1), shows the calibration curve corresponding to the amperometric responses of the system at variable concentrations of lactate. It should be noted that in the applied potential-region the system is not sensitive to glucose in the entire concentration-range, Figure 3B, top (curve 2). The analysis of lactate can be switched on and off by shifting the magnet to positions below and above the working electrode. The selective analysis of each of the substrates by the two biocatalytic systems is impossible without the separation or blocking of one of the catalytic systems. Thus, the selective oxidation of lactate is accomplished by the application of a potential range ($-0.13\text{ V} < E < 0.32\text{ V}$) that stimulates the bioelectrocatalyzed oxidation of lactate, but is not appropriate to activate the bioelectrocatalyzed oxidation of glucose. The selective oxidation of glucose ($E > 0.32\text{ V}$) is then achieved upon the magnetic-field-induced retraction of the aNAD^+ -PQQ-functionalized magnetic particles from the electrode, a process that blocks the bioelectrocatalyzed oxidation of lactate. Thus, the selective analysis of each of the substrates is reversibly accomplished by limiting the potential to a range that is appropriate to activate only one bioelectrocatalytic system, and by the physical separation and blocking of one biocatalytic system using an external magnetic field.

In conclusion, we have demonstrated the use of a relay-modified-electrode, two enzymes, and functional magnetic particles as an integrated system for the programmed analysis of one of two substrates using an external magnet as an actuator.

Experimental Section

Magnetic particles (Fe_3O_4 , saturation magnetization ca. 65 emu g^{-1}), approximately $1\text{ }\mu\text{m}$ average diameter, were prepared according to the published procedure^[15] without including the surfactant into the reaction medium. The magnetic particles (500 mg) were silanized with [3-(2-aminoethyl)aminopropyl]trimethoxysilane, 5% (v/v), in dry toluene for 2 h under reflux.^[7] Pyrroloquinoline quinone (PQQ; **1**, $1 \times 10^{-3}\text{ M}$), was covalently linked to the amino-functionalized magnetic particles (200 mg) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC; $1 \times 10^{-2}\text{ M}$), as a coupling reagent in 0.1M HEPES-buffer, pH 7.2.^[11a] Aminoethyl-functionalized NAD^+ (aNAD^+ ; **2**, $1 \times 10^{-3}\text{ M}$) was covalently linked to the carboxylic groups of the PQQ bound to magnetic particles (200 mg) in the presence of EDC ($1 \times 10^{-2}\text{ M}$) in HEPES-buffer (2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid; 0.1M) pH 7.2.^[13] The Au-electrode surface (ca. 2 cm^2 area) was modified with a monolayer of cystamine,^[11a] and the ferrocene carboxylic acid derivative (Fc; **3**, $1 \times 10^{-3}\text{ M}$) was covalently linked to the amino groups of the cystamine monolayer in the presence of EDC, $1 \times 10^{-2}\text{ M}$, in HEPES-buffer (0.1M), pH 7.2.^[16] The aNAD^+ -PQQ-modified magnetic particles (20 mg) were introduced into an electro-

chemical cell that included the Fc-modified Au-working-electrode, glassy carbon counter electrode and saturated calomel reference electrode (SCE). The potentials in the paper are reported versus SCE. A 5 mm diameter NdFeB/Zn-coated magnet with the remanent magnetization of 10.8 kG was used to move the magnetic particles up and down. The electrochemical measurements were performed using an electrochemical analyzer (EG&G, model 6310) under argon at room temperature.

Received: August 30, 2001

Revised: January 24, 2002 [Z17824]

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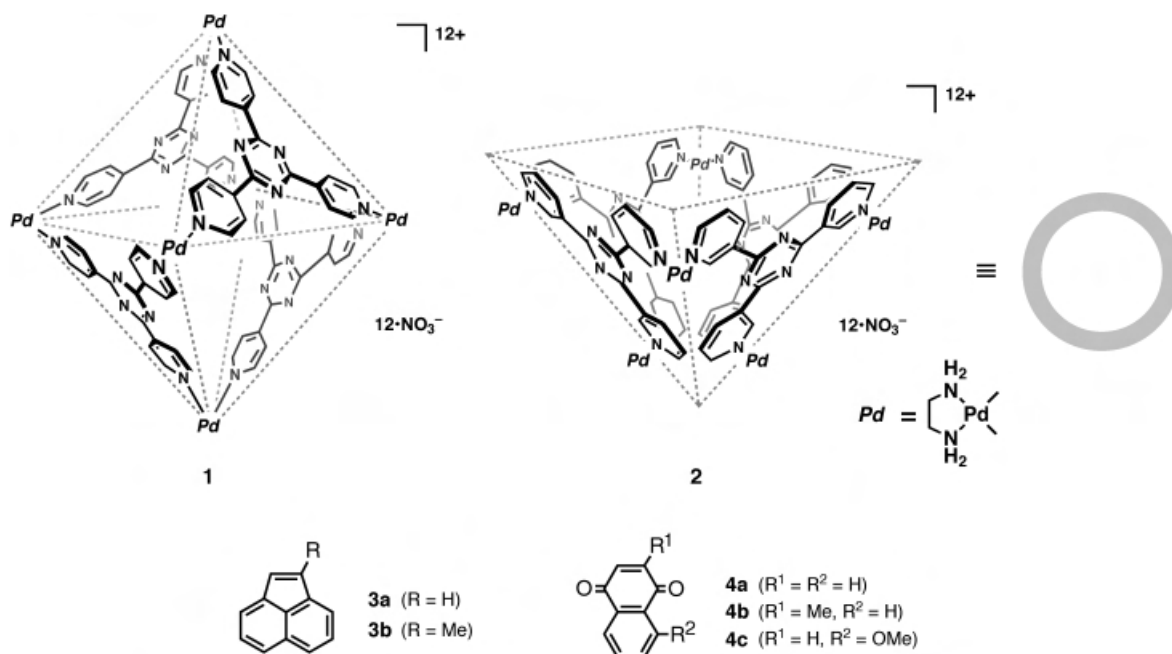
Cavity-Directed, Highly Stereoselective [2+2] Photodimerization of Olefins within Self-Assembled Coordination Cages**

Michito Yoshizawa, Yoshihisa Takeyama, Takahiro Kusakawa, and Makoto Fujita*

Selective encapsulation and isolation of molecules are one of the most attractive features of cage-like molecules.^[1] Intermolecular chemical reactions of two or more substrates encapsulated in a molecular cage can be remarkably accelerated and suitably controlled as a result of the dramatically increased concentration and the strictly regulated orientation of the substrates in the cavity.^[2] Such systems provide artificial mimics of the sophisticated active site of enzymes.^[3] Recently we reported that structurally well-defined coordination cages (**1** and **2**), which self-assemble from six metal ions and four tridentate ligands, selectively encapsulate large organic molecules at the fixed position of the nanosized cavity.^[4,5] Thus, they are expected to facilitate intermolecular [2+2] photochemical reactions and control the stereo- and regiochemistry

in stringent geometrical environment. The photodimerization has been studied extensively in some media such as micelles, zeolites, organic hosts (for example, cyclodextrins and cucurbiturils),^[6] and crystals.^[7] However, a high degree of stereo- and regiochemical control is still desired. Here we report remarkably accelerated, highly stereoregulated [2+2] photodimerization of acenaphthylenes (**3**)^[8] and naphthoquinones (**4**)^[9] within the coordination cages (**1** and **2**) in an aqueous medium that give rise to only *syn* and head-to-tail isomers.

Quantitative formation of a *syn* dimer of acenaphthylene (**3a**) within cage **1** was clearly observed in the following experiment: An excess amount of **3a** was suspended in a solution of **1** in D₂O (2.0 mM) for 10 min at 80 °C. Analysis of the D₂O solution after filtration of free **3a** by ¹H NMR spectroscopy showed formation of the encapsulation complex **1**·(**3a**)₂ had occurred (Figure 1a). The signals of **3a** were highly upfield-shifted as a result of the efficient encapsulation in the cavity. After the clear solution was irradiated (400 W) for 0.5 h at room temperature, the signals derived from **3a** completely disappeared and one set of new signals appeared at δ = 5.84, 5.61, 3.39, and 2.87 (Figure 1b). The signals of **1**



[*] Prof. Dr. M. Fujita
CREST, Japan Science and Technology Corporation (JST)
Department of Applied Chemistry
Graduate School of Engineering, Nagoya University
Chikusa-ku, Nagoya 464-8603 (Japan)
Fax: (+81) 52-789-3199
E-mail: mfujita@apchem.nagoya-u.ac.jp

Dr. M. Yoshizawa, Y. Takeyama, Dr. T. Kusakawa
Department of Applied Chemistry
Graduate School of Engineering, Nagoya University (Japan)

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

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

(δ = 9.28, 8.52, and 2.99; Figure 1a) remained unchanged, which suggests that no decomposition of cage **1** occurred during the irradiation. The product was identified as *syn* dimer **5a** after extraction with CDCl₃, and the yield was estimated to be > 98 % based on **3a** (Figure 1c).^[8,10]

The following experiments revealed that the cavity of cage **1** dramatically accelerated the reaction and strictly controlled the stereochemistry of the product. No reaction took place in benzene (2.0 mM) after 0.5 h in the absence of cage **1**.^[11] At higher concentrations (150 mM, 3 h, in benzene), adducts were formed in low yield with poor stereoselectivity (*syn*: 19%, *anti*: 17%).

The regiochemistry of the [2+2] addition of asymmetrically substituted 1-methylenacenaphthylene (**3b**) [Eq. (1)] was also

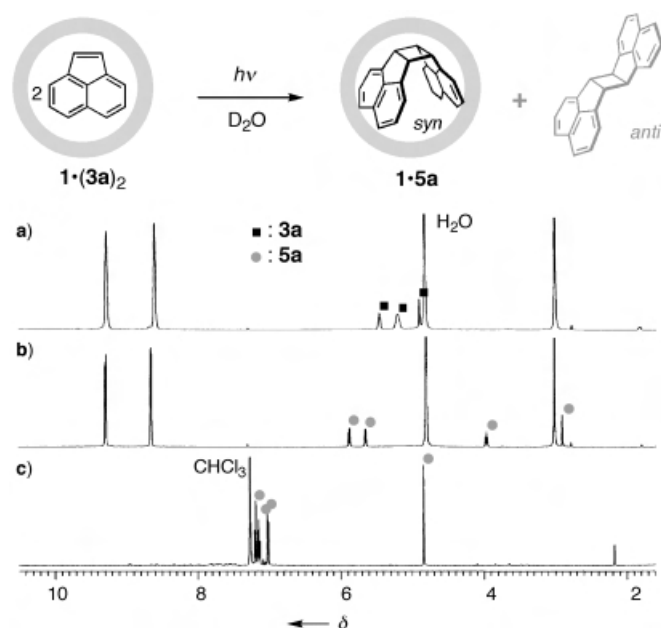


Figure 1. ^1H NMR spectroscopic analysis (500 MHz, D_2O , 27°C) of the photodimerization of **3a** within cage **1**: a) before irradiation ($1 \cdot (3a)_2$) in D_2O ; b) after irradiation (400 W) for 0.5 h; c) after extraction with CDCl_3 .

highly controlled by the cage. The irradiation of the $1 \cdot (3b)_n$ ($n \approx 2$) complex for 3 h at 0.5 mM gave head-to-tail *syn* isomer **5b** in >98% yield without any other regio- and stereoisomers.^[8, 12, 13] The photoirradiation of the sterically demanding substrate **3b** without the cage in benzene no longer gave the adducts, even at a very high concentration (150 mM).



Figure 2. ^1H NMR spectroscopic analysis (500 MHz, D_2O , 27°C) of the photodimerization of **4a** within bowl **2**: a) before reaction ($2 \cdot (4a)_2$) in D_2O ; b) after irradiation (400 W) for 3 h; c) after extraction with CDCl_3 .

The structure of **2·6a** was confirmed by X-ray crystallographic analysis. A single crystal suitable for X-ray analysis was obtained by diffusing acetone into an aqueous solution of **2·6a** at room temperature for 10 days. As expected, the crystal structure showed the dimer **6a** in the *syn* configuration in the cavity (Figure 3). The framework of **2** adopted a box-shaped conformation to nicely accommodate **6a** in the cavity

through aromatic interactions (π - π and $\text{CH}-\pi$ interactions of around 3.5 Å).^[2g] Two aromatic rings of **6a** were pinched by the host and significantly distorted to maximize the host-guest interactions.

The photodimerization of naphthoquinones (**4**) was most effectively controlled by the bowl-shaped coordination host **2**.^[5] Thus, naphthoquinone (**4a**; 5.0×10^{-2} mmol) was added to an aqueous solution (3.0 mL) of **2** (15.0×10^{-3} mmol, 5.0 mM) and the mixture was stirred for 10 min at 80°C to give encapsulation complex $2 \cdot (4a)_n$ ($n \approx 2$; Figure 2a). After filtration of excess **4a**, the resulting solution was irradiated for 3 h at room temperature. The ^1H NMR spectrum of the solution showed very broad signals (Figure 2b) which suggested the conformation of the host's framework was restricted by strong interactions between the host and the guest.^[2g] The ^1H NMR spectrum of the product obtained after extraction with CDCl_3 clearly showed the formation of *syn* dimer **6a** in >98% yield (Figure 2c).^[9, 10] This result strikingly contrasts to that obtained in benzene where the *anti* dimer (21%) was predominantly formed over the *syn* dimer (2%) at a high concentration (50 mM).

The regioselectivity in the photodimerization of 2-methylnaphthoquinone (**4b**) within the cage **1** was very high (96% head-to-tail), while moderate within the bowl **2** (78% head-to-tail).^[9b, 13] Interestingly, the regioselectivity was remote-controlled by a substituent on the naphthalene ring: 5-methoxynaphthoquinone (**4c**) was photodimerized in the bowl **2** with 79% head-to-tail selectivity. The irradiation of **4b** without the cages (50 mM, 3 h, in benzene) did not afford any dimerized products, while that of **4c** gave the *anti* dimer in 21% yield.

The present study has shown that the self-assembled nanocages act as molecular flasks to promote intermolecular [2+2] photodimerization of large olefins in a surprisingly efficient fashion. The cages are readily available and their cavities are extraordinarily large, which makes possible the creation of new chemistry within the localized microspace of discrete molecules.

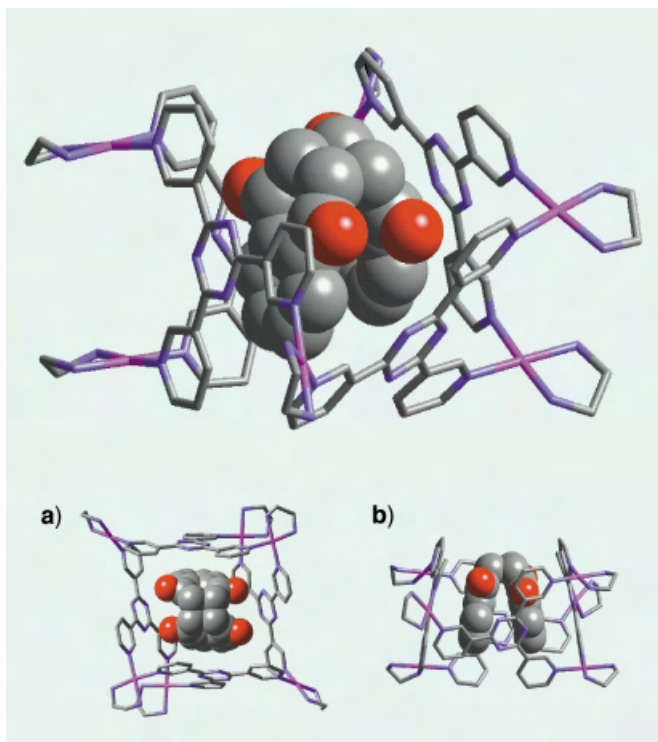


Figure 3. The crystal structure of **2·6a**: a) top view; b) side view.

Experimental Section

Photodimerization of **3a** within coordination cage **1**: Acenaphthylene (**3a**; 6.0 mg, 39.5×10^{-3} mmol) was suspended in a solution (3.2 mL) of **1** (19.3 mg; 6.5×10^{-3} mmol, 2.0 mm) in D_2O and the mixture was stirred for 10 min at $80^\circ C$. After any free **3a** had been filtered off, the clear solution was placed in quartz or Pyrex cells and irradiated with 400 W high-pressure mercury lamp (SEN LIGHTS CORP. HB400X-15) for 0.5 h at room temperature. The solution was extracted with $CDCl_3$ and the product identified as syn dimer **5a** in a yield of > 98 % (by ^1H NMR spectroscopy). The crude product was purified by column chromatography (silica gel) to give **5a** as a colorless solid (1.8 mg, 92 % yield).^[8] Satisfactory spectroscopic data were obtained for **5a**, **1·5a**, and for all the compounds described in this paper (see Supporting Information).

X-ray crystal structure of **2·6a**: Single crystals suitable for X-ray analysis were obtained by diffusing acetone into an aqueous solution of **2·6a** (15.0 mm, 0.5 mL) at room temperature for 10 days. Crystal data for **2·6a**: $C_{104}H_{108}N_{48}O_{40}Pd_6$, $M_r = 3308.78$, crystal dimensions $0.25 \times 0.20 \times 0.20$ mm³, tetragonal space group $P4_32_12$ (no. 96), $a = b = 25.013(3)$, $c = 25.063(5)$ Å, $V = 15680(4)$ Å³, $Z = 4$, $\rho_{calcd} = 1.402$ g cm⁻³, $F(000) = 6656$, radiation, $\lambda(MoK\alpha) = 0.71073$ Å, $T = 113(2)$ K, reflections collected/unique 101179/18140 ($R_{int} = 0.2097$). The structure was solved by direct methods (SHELXL-97) and refined by full-matrix least-squares methods on F^2 with 814 parameters. $R_1 = 0.1061$ ($I > 2\sigma(I)$), $wR_2 = 0.2724$, GOF = 1.046; max/min. residual density 1.652/−1.694 e Å⁻³. Further refinement was unsuccessful because of the high degree of disorder of the counterions and water molecules. CCDC-174264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Received: November 30, 2001 [Z18306]

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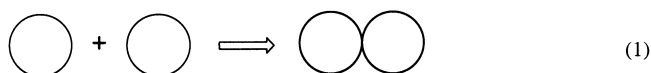
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Adhesive and Anti-Adhesive Agents in Giant Vesicles**

Fredric M. Menger,* Victor A. Seredyuk, and Alexander A. Yaroslavov

Life, it might be said, is a sticky business. Substrate and enzyme; antigen and antibody; tRNA and mRNA; leukocyte and endothelial cell; bacteriophage and bacterium; sperm and egg—all such pairs stick to each other. Sometimes, as with plaque material and arterial walls, stickiness threatens life. Other times, as with a metastasizing cancer cell, it is the absence of a normal stickiness that threatens life. The present paper is devoted to the adhesion between biomembranes comprising giant vesicles. Our goal is to identify agents and mechanisms that promote or impede adhesion between such membranes.^[1]

Although excellent methods exist for studying adhesion between membrane surfaces,^[2] giant vesicles (hollow bilayer spheres 10–100 μm in diameter) offer certain advantages.^[3, 4] First, one can construct surfaces with a known composition and with realistic, cell-like curvatures. Second, and more importantly, one can see adhesion under a light microscope. When two giant vesicles do not adhere, they remain undeformed upon contact [Eq. (1), where the circles represent



cross-sections of the lipid spheres]. When two vesicles strongly adhere, they fuse to create a common boundary [Eq. (2)]. As will be seen, this adhesion can be temporary or permanent, depending upon the bilayer composition and the presence or absence of an agent. Natural and synthetic polymers, in single or multilayers, can also effect adhesive properties.



Single giant vesicles (believed to be unilamellar)^[5, 6] were prepared by electroformation,^[7] manipulated with micropipettes,^[8] and observed in real time by phase-contrast microscopy. When giant vesicles are subjected to mechanical,^[9] thermal,^[10] chemical,^[11] or electrical^[12] alterations, various cytomimetic^[9] events take place. These include fusion, birthing, budding, and endocytosis. Many of these morphological changes are difficult or impossible to observe with

smaller vesicles (30–200 nm), the study of which has, to date, comprised the bulk of vesicle (liposome) research.^[13, 14]

Figure 1 shows what happens when two vesicles fail to adhere after a micropipette places them into direct contact. Vesicle pairs displaying this behavior are of three types: a) Two neutral vesicles composed of 1-palmitoyl-2-oleoylphosphatidylcholine (POPC); b) two positively charged vesicles composed of POPC with 5 mol % of cationic didodecyl-dimethylammonium bromide (DDAB); c) two negatively charged vesicles composed of POPC with 5 mol % of anionic 1-palmitoyl-2-oleoylphosphatidylglycerol (POPG). All experiments were carried out at room temperature, at which the host lipid (POPC) exists in the fluid liquid crystalline phase within vesicles 50–100 μm in diameter.

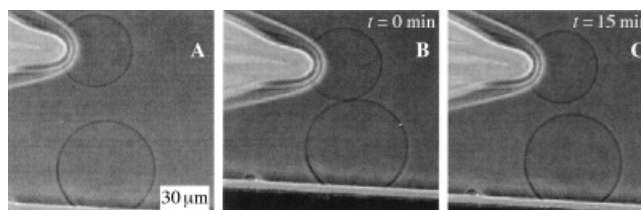


Figure 1. Phase-contrast photomicrographs of POPC vesicles, which are brought into contact with a micromanipulator. The vesicles fail to adhere and drift apart within 15 min. Immediate separation occurs when the micropipette is shifted upward.

Completely different behavior is observed when the two vesicles are of opposite charge (Figure 2). Thus, two distinct populations of vesicles were prepared by coating one Pt wire of the electroformation cell^[7] with negative lipid and the other Pt wire with positive lipid. Application of a 1.0 V, 3.0 Hz alternating current produced giant vesicles on both wires, which could be brought into contact by micromanipulation. The resulting adhesion persists for at least 40 min and the unattached vesicle is free to move and explore the surface of its partner (Figure 2; a behavior that would not be observable by traditional methods, for example, light scattering).

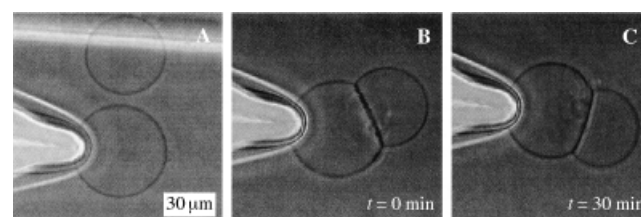


Figure 2. Adhesion between anionic vesicle composed of POPC:POPG (90:10) and a cationic vesicle composed of POPC:DDAB (90:10). Note how the POPC–DDAB vesicle moves about the surface of the POPC–POPG vesicle fixed to the pipette.

Adhesion between oppositely charged vesicles can be prevented by incorporating into both POPC vesicles 10 mole % of 1-palmitoyl-2-oleoylphosphatidylethanolamine, in which the nitrogen was bonded to a 2000 molecular weight polyethylene glycol (PEG). Later experiments showed that this level of polyethylene glycol incorporation in only one of the two vesicles also suffices to prevent adhesion. On the other hand, a 2 mole % polymer-bearing lipid does not

[*] Prof. F. M. Menger, Dr. V. A. Seredyuk
Department of Chemistry
Emory University
Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6586
E-mail: menger@emory.edu

Prof. A. A. Yaroslavov
Department of Polymer Sciences
Moscow State University
119899 Moscow (Russia)

[**] This research was supported by the National Institutes of Health Grant 21457 and Fogarty Grant TWO5555.

prevent adhesion. These observations are reminiscent of the enhanced lifetimes of PEG-protected submicroscopic vesicles in biological fluids.^[15]

An interesting time-dependent adhesion occurs when 20 mole % of 1,2-dioleoyl-phosphatidylethanolamine (DOPE) is included in the POPC bilayer. DOPE was of interest to us because of its tendency to form an inverted hexagonal (H_{II}) phase, which can facilitate membrane fusion.^[16, 17] Adhesion between two oppositely charged vesicle occurs as usual (Figure 3). However, after 10–15 min, the vesicles are seen to lose their adhesion and drift apart. If the DOPE level is reduced to 10 mole %, then the vesicles drift apart only after 25 min.

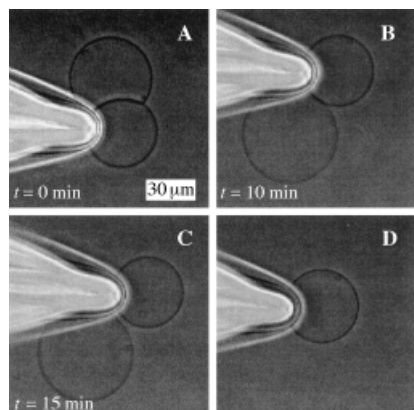
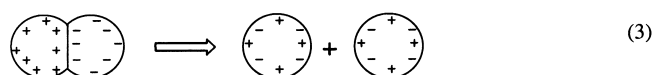


Figure 3. Two oppositely charged vesicles composed of POPC:POPG:DOPE (75:5:20) and POPC:DDAB:DOPE (75:5:20) showing A) adhesion at 0 min; B) reduced adhesion after 10 min; C) complete separation after 15 min; D) diffusion of separated vesicle from field of view.

The simplest explanation is that the DOPE allows the exchange of charged lipids across the common boundary. Once the charge in each membrane becomes neutralized, the vesicles are free to separate [Eq. (3)]. In 1991, Wimley and Thompson^[18] demonstrated that a phosphatidylethanolamine enhances phospholipid exchange among 110 nm vesicles, but Figure 3 is the first visual evidence for such an effect.



Poly-L-lysine, a polycation known to induce morphological changes or rupture in both model and cell-membrane systems,^[19, 20] does not promote adhesion between two neutral POPC vesicles. However, when poly-L-lysine ($0.2 \mu\text{M}$, $M_r = 244 \text{ kD}$) is added to two POPC vesicles rendered anionic with 10 mole % POPG, the vesicles adhere tightly. It is as if the poly-L-lysine acts as an electrostatic glue. One wonders if an imposed selective adhesion might provide a mechanism for confining cancer cells to their primary tumor site.

The preceding served as a prelude to more sophisticated experiments involving two biomedically important macromolecules: polyvinylpyrrolidone (PVP, a nonionic polymer)^[21] and heparin (an anionic polysaccharide).^[22] PVP has a known affinity for anionic compounds,^[23] and heparin interacts with cationic bilayers.^[24]

Entry 2 (Table 1) shows how the addition of PVP ($25 \mu\text{M}$, $M_r = 40 \text{ kD}$) to a mixed sample of anionic and cationic vesicles prevents adhesion. This effect must be caused by a PVP coating (yellow) of the anionic vesicle, because as shown in entry 3 a cationic vesicle (exposed to the PVP in a separate apparatus and then transferred by pipette to an anionic vesicle) does adhere. Two anionic vesicles, both with adsorbed PVP, do not adhere (entry 4). In entry 5, a cationic vesicle was coated with heparin (blue; $1 \mu\text{M}$, $M_r = 3 \text{ kD}$) prior to its introduction to an anionic vesicle. The usual anionic/cationic-vesicle adhesion (entry 1) is thereby prevented.

Table 1. Interactions of anionic and cationic vesicles coated with nonionic PVP (yellow) and anionic heparin (blue).

Entry	Type of interaction	Effect
1		
2		
3		
4		
5		
6		

A double-coating experiment is shown in entry 6: A homogeneous population of anionic vesicles is first exposed to $25 \mu\text{M}$ PVP for 10 min, followed by a $1 \mu\text{M}$ heparin exposure. Vesicle transfer to a separately prepared colony of cationic vesicles produced adhesion. Had the heparin not adsorbed onto the PVP, no adhesion would have occurred (entry 2). Clearly, PVP can effectively bind anionic heparin to anionic vesicles. And heparin can serve as a membrane adhesive (entry 6) or anti-adhesive (entry 5), depending upon the charge properties of the system.

In summary, a series of diverse experiments, in which adhesion is promoted or prevented, demonstrates the utility of giant vesicles in assessing the stickiness of organic substances.

Received: November 30, 2001 [Z18305]

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Electrochemical Modification of Single Carbon Nanotubes**

Steven Earl Kooi, Ulrich Schlecht, Marko Burghard,* and Klaus Kern

Since the discovery of single-walled carbon nanotubes (SWCNTs),^[1] there has been a continuing interest in exploring their physical and chemical properties, as well as in their possible applications.^[2] Some of these applications, for example as mechanically reinforced composite materials or as tips with tailored chemical sensitivity for scanning microscopy, require appropriate chemical modification of the tubes. Unlike for fullerenes,^[3] techniques for the chemical modification of SWCNTs remain limited. This limitation is largely because of their low reactivity, which is thought to be only slightly higher than that of graphite, because of the curvature of their surfaces.^[4] Typically, chemical modification of SWCNTs has involved vigorous oxidation processes that often lead to damage of the tubes.^[5–8] To avoid the harsh conditions of oxidative treatment, milder and more controllable methods with which to introduce polar groups have been developed, including side-wall fluorination^[9, 10] and electrochemical modification.^[11] However, up to now all of these chemical modification methods were performed only on bulk SWCNT material, not on individual tubes.

Herein we describe a versatile approach to the electrochemical modification of individual carbon nanotubes (small SWCNT bundles), as demonstrated by the attachment of substituted phenyl groups. The electrochemical approach is particularly suitable for the chemical alteration of single-molecular objects, as their electrochemical potential, which determines the extent of reaction, can be directly adjusted by an applied potential. Our results show that functional groups can be controllably attached to appropriately contacted nanotubes, which results in homogeneous molecular coatings of up to several nanometers in thickness. We present two types of coupling reactions, working under oxidative (anodic) or reductive (cathodic) conditions. The corresponding electrochemical reactions are illustrated schematically in Figure 1. In both cases a radical species is produced on the surface of the nanotube, which attacks the carbon lattice to form a covalent bond. When the potential is applied for a suitable length of time, polymerization of the radicals leads to multilayer coating. This situation is similar to the multilayer growth of aryl films observed in the electrochemical modification of highly oriented pyrolytic graphite (HOPG).^[12, 13]

To address individual SWCNTs/small bundles electrically, the purified tubes were first deposited on surface-modified Si/

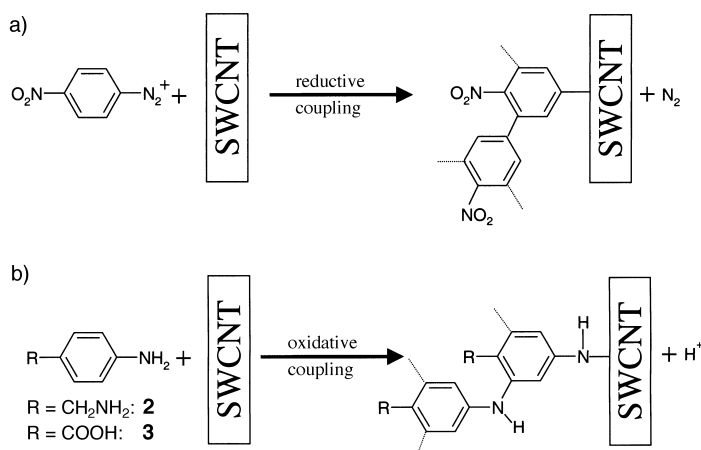


Figure 1. Electrochemical modifications: a) reductive coupling of **1** to SWCNTs, b) oxidative coupling of **2** and **3** to SWCNTs. The dotted lines mark positions of further linkages that could form during the growth of a thicker, polymerized layer of phenyl units on the single-walled carbon nanotube (SWCNT).

SiO₂ substrates, and then contacted with electrodes which had been shaped by electron-beam lithography. Typically, one third of the objects consist of individual SWCNTs, and two thirds are SWCNT bundles with diameters of 3–5 nm. Electrochemical modification was carried out in a home-built miniaturized electrochemical cell, equipped with platinum wires as counter and pseudo-reference electrodes, and with a needle probe to make contact with one of the Au/Pd bonding pads on the Si/SiO₂ substrate. To obtain reproducible deposition conditions, the surface was thoroughly cleaned of any residues from the electron-beam mask prior to applying the potential. Individual SWCNTs and SWCNT small bundles were characterized by atomic force microscopy (AFM) before and after modification. Different degrees of modification could be achieved, depending on the concentration of the coupling species, the duration, and the magnitude of the applied potential.

The cathodic coupling was tested on the reduction of 4-NO₂C₆H₄N₂⁺BF₄⁻ (**1**-BF₄⁻; 1 mM), in DMF and with NBu₄⁺BF₄⁻ as the electrolyte (Figure 1a). In an electrochemical cell, the peak of the irreversible reduction wave of **1**-BF₄⁻, which signifies the formation of the phenyl radical, was observed at a voltage of –1.3 V versus Pt. The same voltage was applied to the deposited SWCNTs for a fixed period of time, typically between 30 s and 2 min, to form a coating thick enough to be detected by AFM. Figure 2a is an AFM image of electrically contacted SWCNTs before the reductive coupling of the 4-nitrophenyl groups. After application of –1.3 V (versus Pt) for 30 s to the left-hand electrode line, only the contacted bundle close to the left margin (marked by the arrow) shows an increase in thickness (Figure 2b). The nanotubes on the right remained unchanged as they were not connected to the current-leading electrode, which demonstrates the selectivity of the method. The height increase of the marked bundle was ~6 nm, determined from the corresponding AFM section profile.

Investigation of the coated tubes by scanning Auger microscopy (10 nm spot diameter of the electron beam)

[*] Dr. M. Burghard, Dr. S. E. Kooi, U. Schlecht, Prof. K. Kern
 Max-Planck-Institut für Festkörperforschung
 Heisenbergstrasse 1, 70569 Stuttgart (Germany)
 Fax: (+49) 711-689-1010
 E-mail: burghard@kern.mpi-stuttgart.mpg.de

[**] This research was supported by the European Union project (no. HPRN-CT-1999-00011). The authors thank B. Siegle (MPI für Metallforschung, Stuttgart) for his help with the Auger measurements.

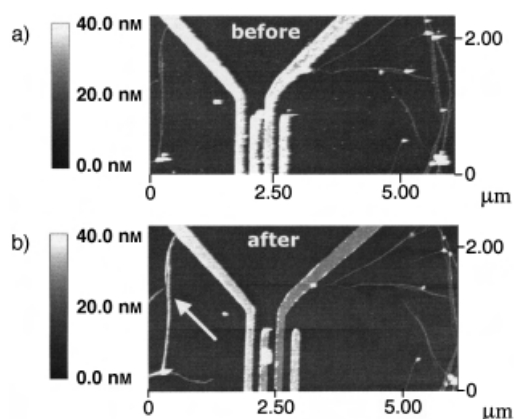


Figure 2. AFM image of SWCNTs before (a) and after (b) reductive coupling with **1**.

revealed an increased nitrogen signal compared to the substrate background. This finding supports the conclusion that the tubes are covered with NO_2 -substituted phenyl groups. In control experiments performed under the same conditions but without 1-BF_4^- , no coating of the nanotubes was observed.

Anodic coupling to SWCNTs was accomplished with two aromatic amines, 4-aminobenzylamine (**2**), and 4-aminobenzoic acid (**3**; Figure 1b). The functional groups of **2** and **3** allow the linking of further molecules, which may facilitate further tailoring of the surface properties of the nanotubes. Oxidative coupling of the amines was carried out in absolute ethanol with LiClO_4 as the electrolyte salt, and the same control experiments were performed as for the diazonium salt (**1**).

The irreversible oxidation wave of **2**, caused by the formation of the radical cation, was observed at +0.85 V (versus Pt) in the bulk electrochemical cell. Figure 3 shows an

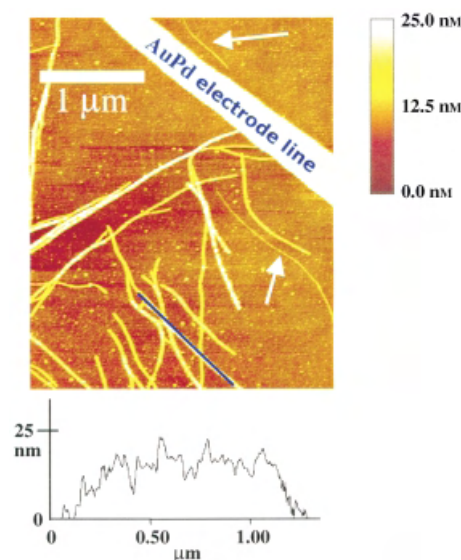


Figure 3. Top: AFM image of SWCNTs after oxidative coupling with **2** (1 mM in $\text{LiClO}_4/\text{ethanol}$) by application of +0.85 V vs. Pt for 90 s. The white arrows mark two individual tubes, which remained unmodified as no conducting path to the electrode line exists. Bottom: AFM height profile of one modified SWCNT bundle is shown (along the blue line in the lower half of the image).

AFM image of SWCNTs after oxidative coupling with **2** by application of this potential for 90 s. All of the SWCNTs in contact with the Au/Pd electrode, or with a close connection to other contacted nanotubes, show an increase in thickness as a result of the deposited layer. After application of +0.85 V (versus Pt) for 30, 60, and 90 s, the corresponding change in the average AFM height of the tubes/bundles before and after modification was found to be 6, 9, and 12 nm, respectively. Similar behavior was observed in the coupling of **3** by using the same electrolyte solution, and a potential of +0.90 V (versus Pt; this is the peak potential of the irreversible oxidation wave observed in the bulk electrochemical cell).

The AFM height profile along one of the modified bundles (Figure 3) reveals that, although the bundle is covered with a closed layer of homogeneous material, the thickness of the coating varies by ± 6 nm. The bundle is rougher than before the modification (by ± 1 nm). The formation of a layer of nonuniform thickness has also been reported in the electrochemical modification of other carbon materials. Both the oxidation of amines^[14] and the reduction of aryl diazonium ions^[13, 15–17] have been investigated as a means of modifying the surface of glassy carbon and HOPG. In these systems, Raman microscopy showed that defects act as reactive sites for the formation of covalent bonds to the carbon lattice,^[18] and a similar function is generally ascribed to defects in carbon nanotubes.^[11] We therefore attribute the roughness of the molecular layer to the attachment of radicals and to radical polymerization starting at defects on the tubes, which results in local deposits that grow in size and finally become interconnected.

The presented method is an approach to the adaptation of the surface chemistry of nano-sized charge-transport channels for use in electrical devices. Electrochemical modification may be useful in transforming metallic SWCNTs into semi-conducting tubes, which are of interest for field-effect devices. The attachment of ligand- or receptorlike functionalities offers the potential of producing nanowires that are compatible with biological structural motifs for applications such as the contacting of nerve cells on a solid support.

Experimental Section

SWCNTs were produced by arc discharge and kindly supplied by P. Bernier (GDPC Montpellier, France). The SWCNTs were dispersed in a surfactant solution (sodium dodecyl sulfate, 1 wt %) and purified by centrifugation.^[19] The resulting suspension was placed on a highly doped Si substrate with a 100 nm thick thermally grown SiO_2 layer, after the surface was treated for 2 min in an aqueous solution of 3-(aminopropyl)triethoxysilane. After an adsorption time of 30 min, the substrate surface was dried in a stream of argon and then rinsed in ultra-pure water and dried again. A standard electron-beam lithography (EBL) procedure was used to deposit electrodes on top of the randomly deposited SWCNTs. Finally, a 1 nm titanium adhesion layer and a 15 nm layer of gold–palladium were evaporated onto the surface of the substrate, to form the electrodes. The substrates were cleaned in DMF for 2 h. The electrochemical experiments were carried out in 0.1 M electrolyte solution, and a Solartron 1285 potentiostat was employed to control the applied potential. AFM images were acquired with a Digital Instruments Nanoscope IIIA microscope operated in tapping mode, which used commercial silicon cantilevers.

Received: September 4, 2001 [Z17850]

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Selective Complexation of *N*-Alkylpyridinium Salts: Recognition of NAD⁺ in Water

Christian Jasper, Thomas Schrader,* Jens Panitzky, and Frank-Gerrit Klärner*

N-Alkylpyridinium salts are widely used in nature in coenzyme-mediated redox processes; the oxidized form of nicotinamide adenine dinucleotide (NAD⁺) formally abstracts a hydride ion from other biomolecules and is converted into its reduced form, NADH. Efficient and selective molecular recognition of this important class of compounds by artificial receptor molecules opens up the possibilities of influencing biological redox processes, alteration of the NAD⁺ redox potential,^[1] targeted transport of NAD⁺, attach-

ment of NAD⁺ to artificial enzymes, and many others. In water, the challenge in constructing such a synthetic receptor molecule was to find a way to replace the highly stable solvation shell around this organic cation with attractive, intermolecular, noncovalent receptor–substrate interactions. Salt bridges alone are not sufficient, because of the energetic costs of anion and cation desolvation. Much more appropriate is the cation– π interaction, because only the cation has to be dehydrated prior to complexation and, in water, this interaction is also supported by the hydrophobic effect.^[2] This major noncovalent force has recently been discovered in numerous natural recognition events^[3] and has been intensively studied by several groups.^[4] These groups found that macrocycles containing aromatic units are able to completely desolvate a number of biologically important organic cations, for example, quaternary ammonium ions,^[5] guanidinium ions,^[6] and *N*-alkylpyridinium ions.^[7] Usually, however, these macrocyclic receptors are not very selective towards their substrate topology. To date, for example, such receptors cannot distinguish between ball-shaped or planar structures.

Molecular clips with planar side walls should be much more shape-selective toward flat structures. Porphyrin clips derived from diphenylglycoluril are capable of complexing *N*-alkylpyridinium cations (for example, viologen cations),^[8] but they also bind to electron-rich aromatic compounds such as pyridine, hydroxypyridine, and phenols.^[9] To date, such clips have been only studied in organic solvents.^[8] Recently, a new molecular clip has been introduced that features two face-to-face naphthalene systems, held apart at a maximum distance of 10 Å by a rigid substituted benzene spacer (Figure 1).^[10, 11]

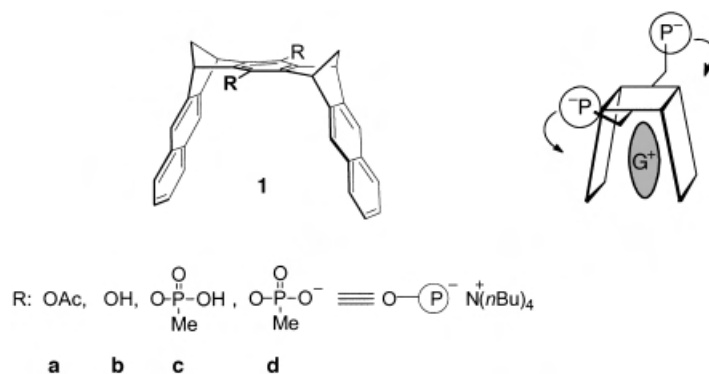


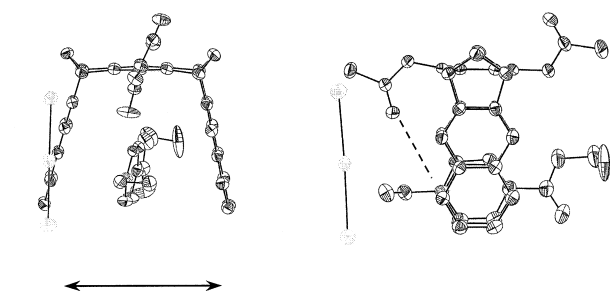
Figure 1. Left: Structures of the molecular clips **1a–d**. Right: Design of the new hybrid receptor system by combination of an electron-rich molecular clip and a bisphosphonate tweezer.

Single-crystal structural analyses of various complexes revealed that the aromatic walls of the clip embrace the substrate molecule tightly, by reducing the distance between the naphthalene tips from about 10 to 8 Å,^[10] as shown in the single-crystal structure of the 1:1 complex between *N*-ethyl-4-carbethoxypyridinium triiodide and the diacetoxy-substituted clip **1a** (Figure 2). Herein, we report the synthesis of the water-soluble molecular clip **1d** and its intriguing receptor properties in aqueous solution.

The synthesis of the clip molecule **1d** began with the reaction of the hydroquinone **1b** with two equivalents of

[*] Prof. Dr. T. Schrader, C. Jasper
 Fachbereich Chemie
 Philipps-Universität Marburg
 Hans-Meerwein-Strasse, 35032 Marburg (Germany)
 Fax: (+49) 6421-282-8917
 E-mail: schrader@mailer.uni-marburg.de
 Prof. Dr. F.-G. Klärner, Dr. J. Panitzky
 Institut für Organische Chemie
 Universität Essen
 Universitätsstrasse 5, 45117 Essen (Germany)
 Fax: (+49) 201-183-4252
 E-mail: klaerner@oc1.orgchem.uni-essen.de

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



$\Delta d = -1.7 \text{ \AA}$ (from 10.0 to 8.3 $\text{\AA}$)

Figure 2. Single-crystal structure of the 1:1 complex between *N*-ethyl-4-carboxypyridinium triiodide and **1a**.^[10]

methylphosphonic acid dichloride, followed by hydrolytic work-up (Scheme 1). The free phosphonic acid **1c** was purified by flash column chromatography and subsequently converted into its tetrabutylammonium salt **1d**. From hydroquinone **2b**, an analogous preparation led to **2d**, which is

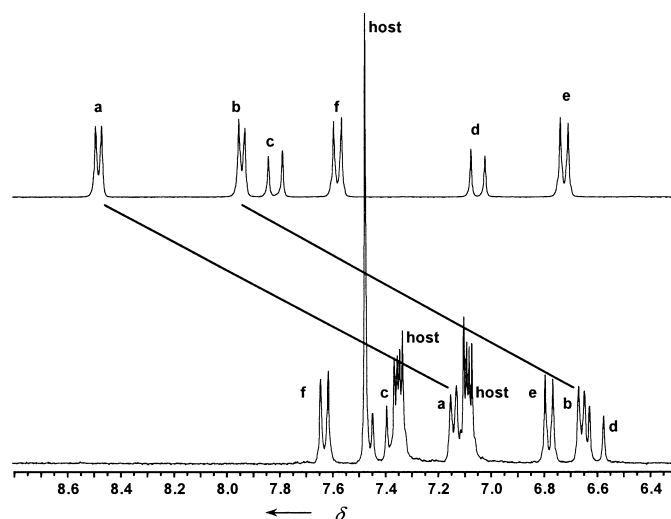
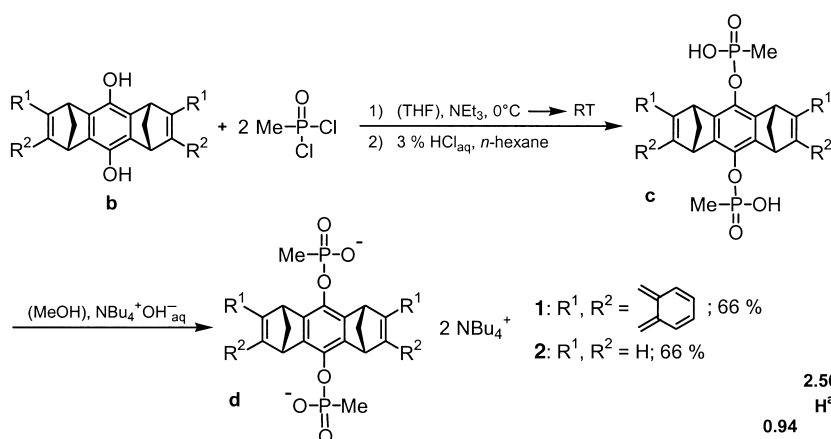


Figure 3. ^1H NMR spectra (aromatic region) of **3** before and after addition of **1d** in methanol. Note the strong upfield shifts of the pyridinium protons a and b (see Scheme 2 for the assignment of the substrate protons).



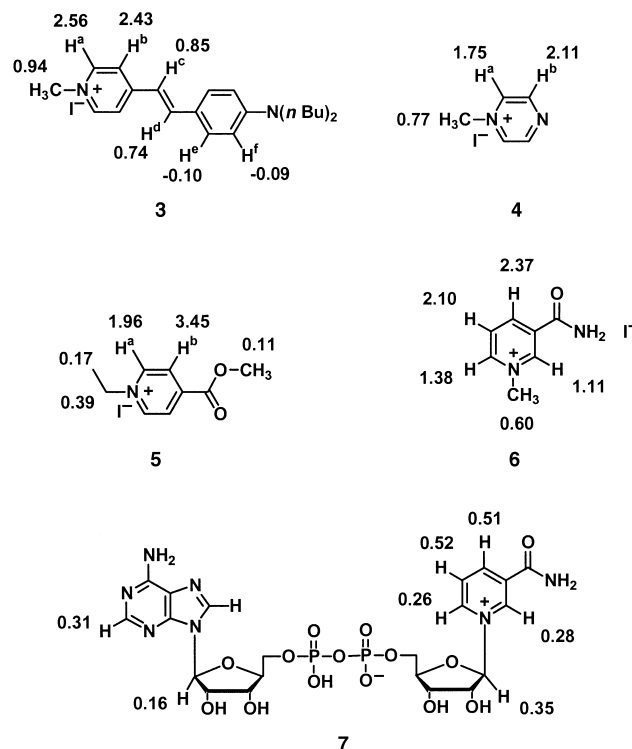
Scheme 1. Synthesis of the molecular clip **1d** and the model compound **2d**.

structurally related to **1d** but lacks the naphthalene walls. This simple model compound (**2d**) served as a reference and an aid in the elucidation of the binding mode of **1d**. Both **1d** and **2d** are very soluble in a wide range of solvents of differing polarities, ranging from chloroform to water.

Clip **1d** combines two powerful noncovalent binding motifs; the clip cavity and the two phosphonate moieties, attached to the hydroquinone spacer unit, which act like the tips of a tweezer. This arrangement mimics the *p*-xylylene bisphosphonates, whose efficiency in ammonium and guanidinium binding is already well established.^[12]

The magnetic anisotropy of the three arene units of **1** makes ^1H NMR spectroscopy a very sensitive probe for detecting the complexation of a substrate molecule inside the cavity of **1**. Stoichiometric (1:1) mixtures of **1d** and the *N*-alkylpyridinium salts **3–7** in methanolic or aqueous solution displayed pronounced complexation-induced upfield shifts of the signals from the substrate protons (Figure 3, Scheme 2), whereas the effect of complexation on the ^1H NMR shifts of the signals arising from the receptor protons is smaller but still significant. This effect is of comparable size in all complexation

studies discussed here, and was therefore employed for the quantitative analysis of the titrations.^[13] The maximum complexation-induced upfield shifts $\Delta\delta_{\text{max}}$, the association constants K_a , and hence the Gibbs enthalpies of complexation ΔG , were determined at 20°C by ^1H NMR dilution titrations, in which the dependencies of the complexation-induced shifts $\Delta\delta$ of the signals from the protons of receptor **1d** on different substrate concentrations were meas-



Scheme 2. Substrate structures and the maximum complexation-induced ^1H NMR upfield shifts ($\Delta\delta_{\text{max}}$) of 1:1 complexes of guests **3–7** with **1d** in water (**3**: methanol).

ured. For the complexation of *N*-methylnicotinamide (**6**) with **1d**, the complex stoichiometry was determined to be 1:1, by use of a Job plot. In each 1:1 mixture of the model compound **2d** with **3–7**, the chemical shifts of the protons of **3–7**, as well as those of **2d**, remained completely unchanged, which indicates that in these cases no complexes were formed.

From the data listed in Table 1, it becomes evident that **1d** forms surprisingly stable complexes with **3–7** in the protic solvents methanol and water compared, for example, with the complex formed between **1a** and the Kosower salt **5** in CDCl_3 , for which the association constant and the complexation-induced shifts in ^1H NMR resonance signals were determined by titration to be $K_a = 137 \pm 14 \text{ M}^{-1}$ ($\Delta G = -2.9 \pm 0.1 \text{ kcal mol}^{-1}$), and $\Delta\delta_{\text{max}} = 1.82$ (**5**; H^a) and 2.40 (**5**; H^b) at 21°C , which indicates a moderate stability. The observation that the complexes formed in water ($K_a = 4800\text{--}12700 \text{ M}^{-1}$)

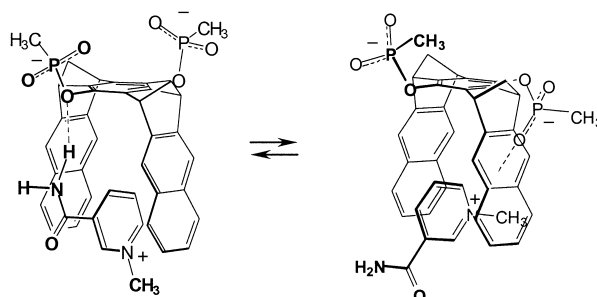
Table 1. Association constant K_a and Gibbs enthalpy of association ΔG for complex formation between **1d** and **3–7**, determined by ^1H NMR dilution titrations in methanol and water at 20°C .

Substrate	$K_a [\text{M}^{-1}]^{[a,b]}$ in CD_3OD	$-\Delta G$ [kcal mol $^{-1}$]	$K_a [\text{M}^{-1}]^{[a,b]}$ in D_2O	$-\Delta G$ [kcal mol $^{-1}$]
3	4000 ± 990	4.8	broad signals ^[c]	–
4	600 ± 30	3.8	9400 ± 2260	5.3
5	3200 ± 350	4.7	4800 ± 720	4.9
6	6900 ± 540	5.2	12700 ± 3840	5.5
7	precipitation ^[c]	–	6500 ± 620	5.1

[a] Determined from the complexation-induced shifts of the same three (in CD_3OD : the same four) receptor signals. In some cases, the analysis of the dependence of $\Delta\delta$ of substrate protons on the concentration of **1d** produced larger K_a values than the concentration dependence of the signals of **1d**; the given values represent the lowest limits for all binding constants. [b] The given errors are standard deviations between the K_a values from different NMR signals; the standard deviations from the nonlinear regressions were consistently lower. [c] Precipitation of the complex after mixing **1d** and **7**, or broad signals in the ^1H NMR spectrum of a mixture of **1d** and **3**, prevented the determination of K_a .

are even more stable than the corresponding ones formed in methanol ($K_a = 600\text{--}6900 \text{ M}^{-1}$) is good evidence for the substantial contribution of hydrophobic interactions in the receptor–substrate binding processes observed here. This observation implies that, especially in water, it is the cation– π interactions and not the salt bridges that are largely responsible for complex stability. A distinct downfield shift of the resonance signal arising from the methyl group of the phosphonate in **1d** (0.2–0.4 ppm) on substrate complexation, indicates the participation of the phosphonate functions in the binding process. This is further supported by a drastic salt effect; in 0.5M aqueous tetrabutylammonium bromide, the binding constant between **1d** and **6** dropped to almost zero.

The complexation-induced ^1H NMR shifts of the substrate protons constitute a very sensitive probe of the complex structure. For example, in the dye **3**, the resonance signals arising from the pyridinium-ring protons show a large upfield shift, whereas the position of the signals arising from the amino-substituted benzene moiety protons remains almost unchanged, indicating that only the pyridinium ring is included inside the cavity of **1d**. To understand why the complex **6@1d** is more stable than that of the structurally related **5@1d**, one can assume that the amide functionality in **6** may serve as an additional binding site (Scheme 3).



Scheme 3. Two low-energy structures and relative energies ΔE_{rel} (kcal mol $^{-1}$) of the complex **6@1d** calculated by the force-field AMBER* (H_2O) with a Monte Carlo simulation (MacroModel 7.0).

Encouraged by the results of the work with **6**, we investigated whether **1d** is also capable of forming a complex with NAD^+ (**7**) as substrate. In methanol, the complex precipitated. In water, no precipitation occurred, and distinct upfield shifts were observed in the signals arising from the protons of the nicotinamide subunit as well as in the adenine nucleoside of NAD^+ (Scheme 2), which unambiguously indicates complex formation between **1d** and **7**. A Monte Carlo simulation (MacroModel 7.0, Amber* force field^[14]) leads to an energy-minimized structure of the complex **7@1d** in water, in which the nicotinamide moiety is inside the clip cavity and the adenine subunit is bound to one naphthalene side wall of **1d** (Figure 4). This double-sandwich structure

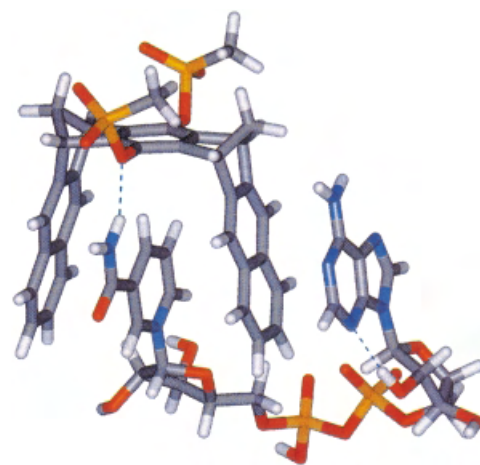


Figure 4. Structure of the complex in water between **7** and **1d** according to Monte Carlo simulations (MacroModel 7.0; AMBER*). During minimization of the energy of the complex structure, the distance between the naphthalene tips decreases from 9.7 to 7.3 Å.

explains why the proton signals of both subunits are shifted upfield in the ^1H NMR spectrum of the complex **7@1d**. Additional evidence for this structure comes from the relatively strong upfield shifts of the resonance signals from the protons in the sandwiched naphthalene walls of **1d** ($\Delta\delta_{\text{max}} = 0.54$ and 0.56 ppm; the average values lie between 0.2 and 0.4 ppm), which are greater than those of all other complexes. Thus, additional π -stacking and van der Waals interactions may be participating. This arrangement bears

some similarity to the natural environment of NAD^+ , which is bound in a well-defined region called the "Rossmann fold"^[14] in most dehydrogenases. Adenine and nicotinamide are both buried in cavities with at least one hydrophobic side.

The K_a value for the formation of the complex **7**@**1d** is smaller than that for **6**@**1d** (Table 1); this is consistent with the fact that the anomeric region of ribose in **7** is sterically more demanding than the methyl group in **6**. In the future we plan to optimize the receptor design for highly efficient and selective NAD^+ recognition in water, for example, by eliminating one of the phosphonate moieties in **1d**, and replacing it with a neutral binding site for ribose.

We have created a molecular clip which binds *N*-alkylpyridinium ions very effectively in water. To our knowledge, this is the first time that NAD^+ has been complexed by a synthetic receptor molecule. Since not every primary *N*-alkylammonium ion is bound in methanol or water, clip **1d** is also the first artificial host that binds only to flat heteroaromatic cations such as *N*-alkylpyridinium derivatives, most other synthetic receptors for these species have a macrocyclic structure and can also accommodate quaternary ammonium salts. Although the molecular clip presented here is obviously not suited for the molecular recognition of sp^3 -hybridized ammonium ions, the related molecular tweezers, which are able to bind dialkylammonium salts in organic solvents,^[15] are promising candidates for this purpose.^[16]

Received: September 19, 2001 [Z17918]

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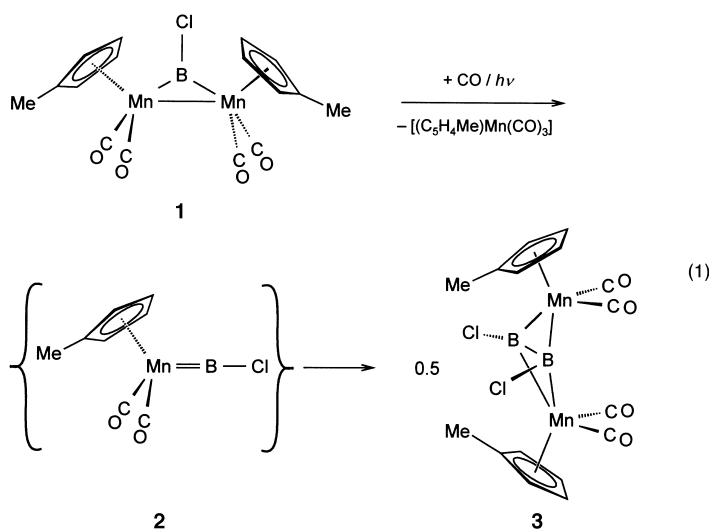
From Classical to Nonclassical Metal–Boron Bonds: Synthesis of a Novel Metallaborane**

Holger Braunschweig,* Miriam Colling, Chunhua Hu, and Krzysztof Radacki

Metallaboranes and borylene complexes are related to some extent as they both display direct metal–boron bonds—the nature of these interactions, however, is diverse. The borylene ligands BR are linked to one or two transition metal centers by classical, electron-precise, two-center two-electron (2c–2e) bonds, whereas the cluster skeleton of a metallaborane is made up by nonclassical, electron-deficient, multicenter two-electron bonds.^[1] While metallaboranes constitute a long known and well established class of transition metal–boron compounds comprising several hundreds of examples,^[2] both bridged^[1b] and terminal borylene complexes were realized only very recently and are still rare—in the case of the latter only five structurally authentic examples were reported since 1998.^[1d,3] Despite the enormous variety of metallaboranes, certain structural motifs, such as the four-vertex *nido*-deltahedron are still unknown. Our investigations on borylene complexes now provided the first synthetic link between these two classes of metal–boron compounds, and thus give access to an unprecedented “butterfly”-shaped *nido*-metallaborane.

Irradiation of the bridged chloroborylene complex $[\mu\text{-BCl}\{(\eta^5\text{-C}_5\text{H}_4\text{CH}_3)\text{Mn}(\text{CO})_2\}_2]$ (**1**)^[4] in hexane under an atmosphere of CO at -30°C afforded complex **3** (yield 37%, orange, crystalline, air sensitive solid) and $[(\eta^5\text{-C}_5\text{H}_4\text{CH}_3)\text{Mn}(\text{CO})_3]$ [Eq. (1)]. Although the detailed mechanism for the formation of **3** is unknown as yet, the terminal chloroborylene complex **2** appears to be a likely transient intermediate, formed by addition of CO to a $[(\eta^5\text{-C}_5\text{H}_4\text{CH}_3)\text{Mn}(\text{CO})_2]$ moiety of the starting material, and then dimerizes to the final product. This assumption is supported by the absence of further boron-containing products (by ^{11}B NMR spectroscopy) and the stoichiometric formation of methylcymantrene $[(\eta^5\text{-C}_5\text{H}_4\text{CH}_3)\text{Mn}(\text{CO})_3]$, which was identified by ^1H and ^{13}C NMR spectroscopy.

The photochemistry of **1** observed here is significantly different from that of terminal aminoborylene complexes of the type $[(\text{OC})_5\text{M}=\text{B}=\text{NR}_2]$, which at -30°C undergo a photochemically induced transfer of the aminoborylene



$\text{B}=\text{NR}_2$ to another metal center, for example chromium.^[3d] Irradiation of **1** in the presence of $[(\text{OC})_5\text{ML}]$ ($\text{M}=\text{Cr}, \text{Mo}, \text{W}$; $\text{L}=\text{CO}, \text{NMe}_3$) under identical conditions gave no evidence for a transmetalation of chloroborylene $\text{B}-\text{Cl}$, but the Group 6 carbonyl complexes were found to act as a source for CO, thus affording **3** as the only boron-containing species, however, in significantly lower yields.

Compound **3** readily dissolves in all common aliphatic or aromatic hydrocarbons. In solution, the ^1H and ^{13}C NMR spectra display single sets of signals for the two $[(\eta^5\text{-C}_5\text{H}_4\text{CH}_3)\text{Mn}(\text{CO})_2]$ moieties and a strongly deshielded resonance signal at $\delta=142.2$ is observed in the ^{11}B NMR spectrum which resembles that of the borylene precursor **1** at $\delta=133.5$. It should be noted though, that unbridged B_2X_2 moieties, which are only known from very few metal-rich metallaboranes with $\text{X}=\text{H}$, are also characterized by considerably downfield shifted ^{11}B NMR signals in the range of $\delta=104\text{--}114$.^[5]

X-ray structure analyses were carried out for both **3** and **1** (Figure 1),^[6,7] since the latter was previously only character-

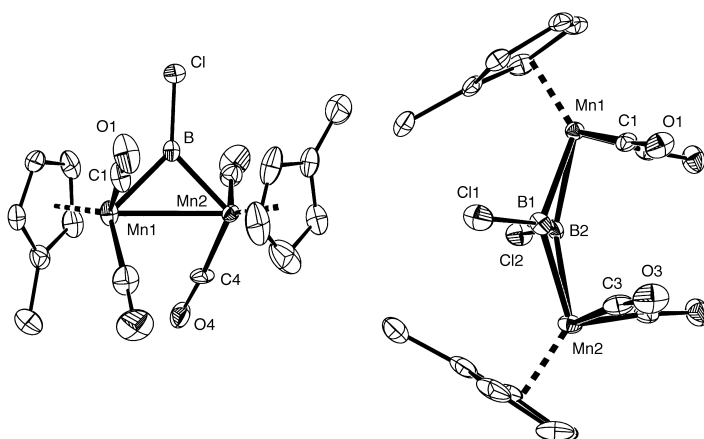


Figure 1. Structures of **1** (left) and **3** (right) in the crystal. Selected distances [Å] and angles [$^\circ$]: **1**: Mn1–B 2.039(11), Mn2–B 1.976(9), Mn1–Mn2 2.8236(15), Mn1–B–Mn2 89.4(4); **3**: Mn1–B1 2.071(6), Mn1–B2 2.072(5), Mn2–B1 2.079(6), Mn2–B2 2.084(6), B1–B2 1.695(7), B1–Cl1 1.804(6), B2–Cl2 1.788(6); Mn1–B1–Mn2 124.3(3), Cl1–B1–B2 148.8(5).

[*] Dr. H. Braunschweig, Dr. K. Radacki
Department of Chemistry
Imperial College
London SW7 2AY (UK)
Fax: (+44)20-7594-5900
E-mail: h.braunschweig@ic.ac.uk.

M. Colling, Dr. C. Hu
Institut für Anorganische Chemie
Technische Hochschule Aachen
52056 Aachen (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, EPSRC, and the Royal Society. We are grateful to the Rechenzentrum of Aachen University of Technology (RWTH) for generously placing computation time at our disposal. HB thanks Prof. Dr. T. P. Fehner (Notre Dame) for helpful discussions.

ized in solution.^[4] The chloroborylene complex **1** crystallizes in the orthorhombic space group $P2_12_12_1$ and exhibits a disorder of one Mn atom, one CO group, and the BCl moiety over two positions with equal occupancy, which accounts for slightly higher standard deviations. The central three-membered ring of **1** has B–Mn bonds of 2.039(11) and 1.976(9) Å, and a Mn–Mn bond of 2.8236(15) Å, thus matching the geometries of the related complexes $[\mu\text{-BOEt}\{\eta^5\text{-C}_5\text{H}_4\text{CH}_3\}\text{-Mn}(\text{CO})_2\}_2]$ and $[\mu\text{-BNMe}_2\{\eta^5\text{-C}_5\text{H}_5\}\text{Mn}(\text{CO})_2\}_2]$.^[4, 8]

Compound **3** crystallizes in the monoclinic space group $P2_1/c$ and has approximate C_{2v} symmetry. The central Mn_2B_2 skeleton displays a bicyclobutane or “butterfly” geometry with a dihedral angle of 150.9° between the two MnB_2 triangles. This particular geometry together with a rather short B–B bond of 1.695(7) Å^[9] and the two boron-bound Cl ligands in *exo*-position supports the description of **3** as a dimetalla-*nido*-tetraborane derived from the corresponding trigonal-bipyramidal *closo*-species by formal elimination of an equatorial vertex—and indeed, **3** fulfills the electron counting rules for a *nido*-compound.^[10] A tetrahedral arrangement of the Mn_2B_2 skeleton, which is adopted by certain four-vertex *nido*-clusters as an alternative to the bicyclobutane structure,^[11] can be ruled out from the large Mn–Mn separation of 3.670 Å.^[12] The Mn–B separations of 2.079(6) and 2.084(6) Å are slightly larger than those in **1** (2.039(11) and 1.976(9) Å), thus accounting for the increased coordination numbers of the boron and manganese atoms. While related four-vertex metalla-*nido*-boranes are unknown, the structures of various aza-*nido*-tetraboranes of the type NB_3R_6 (R = H, alkyl) were reported over the past decade, all being characterized by the same “butterfly” geometry.^[13]

Self-consistent field (SCF) calculations^[14] on **3** converged for a C_{2v} symmetrical geometry, which frequency analysis confirmed to be a minimum. The calculated structural parameters of **3** are in good agreement with the experimental data (Table 1), and show only slightly larger interatomic distances (0.001–0.015 Å) than those reported for calculations on other transition metal–boron compounds.^[3e, 15] An exception, however, is the B–B bond, which was calculated to be 0.02 Å shorter than in the crystal structure. The Mn1–B1–B2–Mn2 dihedral angle was found to be 149.0°, thus being 1.1° more acute than in the crystal, which together with slightly longer B–Mn distances results in almost the same Mn–Mn separation.

Gauge independent atomic orbitals (GIAO) chemical shifts for ¹H and ¹³C nuclei match the experimental data (Table 1), however, the calculated ¹¹B NMR resonance signal is deshielded by 26 ppm. Both this discrepancy and the shorter B–B distance is probably a consequence of the smaller CEP-31 basis used for manganese.

The Wiberg bond index (WBI) for Mn–Mn is close to zero and indicates no interaction between the two metal centers. The WBI for B–B, however, was calculated to be 0.8 and thus suggests a strong boron–boron interaction. The natural bond orbital (NBO) analysis^[16] gives no evidence for 2c–2e bonds between any of the four central atoms, but rather a 3c–2e Mn–B–B bond with a 27%:37%:37% composition.

Experimental Section

3: **1**^[4] (0.44 g, 1.03 mmol) was dissolved in hexane (130 mL) under an atmosphere of CO. The mixture was irradiated with a high-pressure Hg lamp (Heraeus TQ 150) at –30 °C for 6 h while gaseous CO was continuously conducted through the solution, the color of which gradually turned from red to orange. The orange reaction mixture was allowed to come to ambient temperature and filtered under a nitrogen atmosphere. The filtrate was concentrated in high vacuum (0 °C/0.001 Torr) to 20 mL and stored at –30 °C. After 3 days **3** (0.09 g, 0.19 mmol, 36.8%) was obtained as small orange crystals.

All NMR spectra were recorded in $[\text{D}_6]\text{benzene}$ at 25 °C. ¹H NMR (500 MHz, TMS): δ = 1.44 (s, 6H, $\text{C}_5\text{H}_4\text{CH}_3$), 4.16, 4.22 (2m, 8H, $\text{C}_5\text{H}_4\text{CH}_3$); ¹¹B NMR (160 MHz, $\text{Et}_2\text{O} \cdot \text{BF}_3$): δ = 142.4; ¹³C NMR (126 MHz, TMS): δ = 13.1 ($\text{C}_5\text{H}_4\text{CH}_3$), 90.5, 90.8 ($\text{C}_5\text{H}_4\text{CH}_3$), 106.2 (ipso-C, $\text{C}_5\text{H}_4\text{CH}_3$), 220.6 (CO); IR (toluene): $\tilde{\nu}$ = 2000, 1951 cm^{-1} (CO); MS m/z = 472 [M^+], 444 [$M^+ - \text{CO}$], 416 [$M^+ - 2\text{CO}$], 388 [$M^+ - 3\text{CO}$], 309 [$M^+ - 3\text{CO} - \text{C}_5\text{H}_4\text{CH}_3$], 263 [$M^+ - 3\text{CO} - \text{C}_5\text{H}_4\text{CH}_3 - \text{BCl}$], 180 [$(\text{C}_5\text{H}_4\text{CH}_3)\text{MnBCl}$], 134 [$(\text{C}_5\text{H}_4\text{CH}_3)\text{Mn}$], 79 [$\text{C}_5\text{H}_4\text{CH}_3$], 55 [Mn]; elemental analysis (%) calcd for $\text{C}_{16}\text{H}_{14}\text{B}_2\text{Cl}_2\text{Mn}_2\text{O}_4$: C 40.66, H 2.99; found: C 40.35, H 2.80.

Received: November 5, 2001 [Z18155]

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Table 1. Selected experimental and calculated spectroscopic and structural data for **3**.

	$\delta(^1\text{H})$ ^[a]	$\delta(^{11}\text{B})$	$\delta(^{13}\text{C})$	B–B [Å]	Mn–B [Å]	B–Cl [Å]	B–B–Cl [°]	Mn–B–B–Mn [°]
exp	1.44, 4.16, 4.22 ^[a]	142.4	13.1, 90.5, 90.8, 106.2, ^[a] 220.6 ^[b]	1.695(7)	2.071(6), 2.072(5), 2.079(6), 2.084(6)	1.804(6), 1.788(6)	148.8(5), 148.1(4)	150.1
calcd	1.28, 3.91, 4.23 ^[a]	168.9	11.9, 80.9, 86.0, 108.5 ^[a] , 223.3 ^[b]	1.676	2.084	1.809	147.6	149.0

[a] Values for $\text{C}_5\text{H}_4\text{CH}_3$, [b] Values for CO.

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- [7] Crystal data for **3**: $C_{16}H_{14}B_2Cl_2Mn_2O_4$, $M_r = 472.67$, crystal dimensions $0.32 \times 0.20 \times 0.02 \text{ mm}^3$, monoclinic, space group $P2_1/c$ (No. 14), $a = 15.5756(18)$, $b = 7.9087(9)$, $c = 15.034(3) \text{ \AA}$, $\beta = 102.045(13)^\circ$, $V = 1811.1(5) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.733 \text{ g cm}^{-3}$, $2\theta_{\text{max}} = 52^\circ$, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$, $\omega/2\theta$ scans, $T = 213(2) \text{ K}$, $\mu = 1.708 \text{ mm}^{-1}$. Of 4338 collected reflections, 3556 were unique ($R_{\text{int}} = 0.0455$). LP and empirical (psi scans) absorption corrections were applied. The structure was solved by direct methods and refined using SHELXTL.^[17] Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were placed in idealized positions ($\text{C-H} = 0.98 \text{ \AA}$ and included as riding with $U_{\text{iso}}(\text{H}) = 1.3 U_{\text{eq}}$ (non-H). $R = 0.0526$ ($I > 2\sigma(I)$), $R_w = 0.0983$ (F^2 , all data), 235 parameters, final difference map extremes 0.509 and $-0.480 \text{ e \AA}^{-3}$. CCDC-173229 (**1**) and -173230 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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Enantioselective C–C Bond Formation with Titanium(IV) Alkoxides—an Unusual Alkylation**

Rainer Mahrwald*

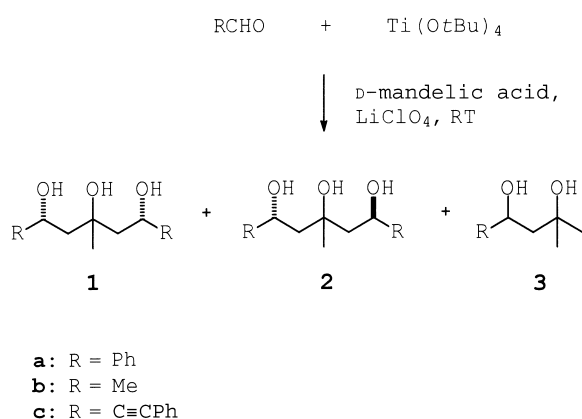
Recently we described an enantioselective aldol reaction of aldehydes with unactivated ketones mediated by titanium(IV) alkoxide ligand exchange.^[1] In attempts to optimize this reaction further by catalytic control, metal salts, among other things, have been used as additives in the aldol reactions. In particular the use of lithium salts has been described by a number of authors in different C–C bond formation processes,^[2] and the use of lithium perchlorate in the Mukaiyama reaction has been known for some time.^[3] Lithium perchlorate is also used in enantioselective aldol reactions. Here a weakening or a cleavage of the metal alkoxide–aldolate bond is assumed. The aldols formed are thus continuously released from the catalyst,^[4] and in this way catalytic control of the reaction is achieved in many cases.^[5]

In our investigations on catalytic aldol addition we observed an activation of the aldehyde in the absence of the ene component (ketone): under the reaction conditions described (LiClO₄, Ti(OtBu)₄, α -hydroxy acids, RT) the aldehydes themselves react with the ligands of the Ti(OtBu)₄ in an alkylation-type reaction. After the initial conversion of benzaldehyde and Ti(OtBu)₄ the *meso* compound **1a**, the *anti* triol **2a**, and the monoaddition product **3a** (Scheme 1) were isolated. The structure of the compounds was determined by nuclear Overhauser enhancement (NOE) difference measurements.^[6] By the addition of D-mandelic acid in this experiment the *anti*-triol **2a** was obtained in enantiomeric excesses of $> 85\%$,^[7] whereas in contrast the diol **3a** was isolated as the racemate. (The *meso* compound **1a** is optically inactive.)

The formation of compounds **1a**, **2a**, and **3a** is dependent upon the amount of D-mandelic acid used. With one

[*] Priv.-Doz. Dr. R. Mahrwald
Institut für Organische und Bioorganische Chemie
Humboldt-Universität Berlin
Brook-Taylor-Strasse 2, 12489 Berlin (Germany)
Fax: (+49) 030-2093-7266
E-mail: rainer.mahrwald@rz.hu-berlin.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft.
 Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



Scheme 1. Reaction of aldehydes with $\text{Ti}(\text{OtBu})_4$ in the presence of LiClO_4 and D-mandelic acid.

equivalent of D-mandelic acid relative to $\text{Ti}(\text{OtBu})_4$ the *meso*, *syn* triol **1a** is formed as the main product (kinetic control). After subsequent equilibration^[8] (2 days, RT) the optically active *anti* triol **2a** is formed as the main product. With four equivalents of D-mandelic acid the diol **3a** is isolated as the main product (Table 1).

Table 1. Reactions of aldehydes with $\text{Ti}(\text{OtBu})_4$ in the presence of D-mandelic acid.

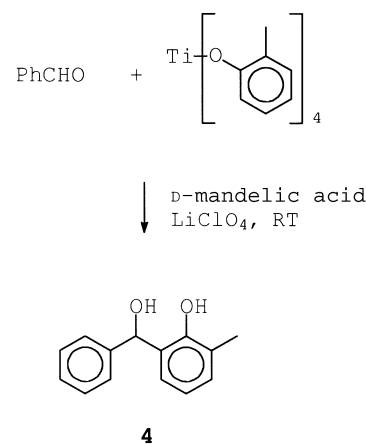
	Aldehyde	Product	Yields [%]			<i>ee</i> [%] [b]
			[a]	[b]	[c]	
1	Ph-CHO	1a	65	5	7	84
2		2a	12	68	13	
3		3a	5	7	64	
4	Me-CHO	1b	43	15	–	65
5		2b	8	36	8	
6		3b	2	–	51	
7	Ph≡-CHO	1c	55	25	–	78
8		2c	11	28	11	
9		3c	4	5	53	

[a] Procedure A (see Supporting Information): freshly distilled aldehyde (10.0 mmol) under argon was added at room temperature to a solution of LiClO_4 (10.0 mmol) in $\text{Ti}(\text{OtBu})_4$ (10.0 mmol). After 15 min D-mandelic acid (10.0 mmol) was added; stir for 24 h. [b] Equilibration, 2 days, RT.^[8] [c] Procedure B (see Supporting Information): as procedure A, only 40.0 mmol D-mandelic acid; stir for 24 h. The ratios of compounds **1**, **2**, and **3** were determined by integration of suitable signals in the ^1H NMR spectra (e.g. $\text{RCH}(\text{OH})\text{CH}_2$).

These surprising results were investigated for their general applicability. Both aromatic and aliphatic aldehydes react according to Scheme 1, and the reaction is dependent upon the carbonyl activity of the aldehyde used. Longer reaction times and lower yields were observed with α -branched aldehydes (R = *t*Bu, 8 days, RT, yield 10%).

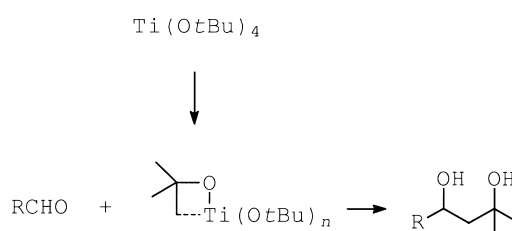
Not all the metal salts used were able to induce this reaction. LiClO_4 was the most efficient. No consistent reactions were observed with the use of $\text{Ba}(\text{ClO}_4)_2$, LiCF_3SO_3 , and $\text{Mg}(\text{ClO}_4)_2$. The use of NaClO_4 , $\text{Mg}(\text{CF}_3\text{SO}_3)_2$, MgBr_2 , Na_2SO_4 , LiCl , LiF , and NEt_4ClO_4 gave no reaction. These results indicate the selective involvement of hard cations (e.g. Li^+). Similar results were obtained by Evans et al in enantioselective aldol reactions.^[5]

After the reaction of the aldehydes with $\text{Ti}(\text{OiPr})_4$ the expected products (secondary alcohols) were only obtained in very low yields. The main products here were the corresponding alcohols formed by reduction. This result is attributed to the pronounced tendency of the secondary titanium(IV) alkoxides to undergo Meerwein–Ponndorf–Verley reduction. Other titanium(IV) alkoxides containing a quaternary carbon atom are more suitable for this reaction. The reaction of benzaldehyde with titanium(IV) *o*-methylphenolate in the presence of D-mandelic acid and LiClO_4 affords the diol **4** (yield 62%) in enantiomeric excesses >88% (Scheme 2). This method thus provides simple and rapid access to optically active saligenol derivatives.^[9]



Scheme 2. Reaction of benzaldehyde with titanium(IV)-*o*-methylphenolate in the presence of LiClO_4 and D-mandelic acid at room temperature.

The reaction mechanism is still unexplained. Enol structures cannot be involved in these reactions as the conversions with $\text{Ti}(\text{OtBu})_4$ show. A C–H activation occurring under the mild reactions conditions described could induce this reaction. Scheme 3 illustrates a proposed mechanism. The C–H activations of *tert*-butyl groups by palladium catalysis have already been described.^[10]



Scheme 3. Proposed mechanism for the reaction of aldehydes with $\text{Ti}(\text{OtBu})_4$ in the presence of LiClO_4 and D-mandelic acid at room temperature. Oxa-2-titana-cyclobutanes were assumed to be the reactive species.

Because of the considerable preparative value and utility of the reactions described here, which must operate for similar C–H activation processes, these results are of great significance.^[11] Investigations aimed at understanding the mechanism and extending this reaction are underway.

Received: October 30, 2001
 Revised: December 18, 2001 [Z18133]

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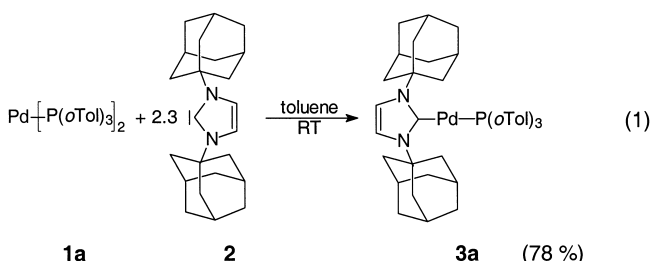
A Defined N-Heterocyclic Carbene Complex for the Palladium-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides at Ambient Temperatures**

Christian W. K. Gstöttmayr, Volker P. W. Böhm, Eberhardt Herdtweck, Manja Grosche, and Wolfgang A. Herrmann*

Dedicated to Prof. Dr. Gottfried Huttner on the occasion of his 65th birthday

The Suzuki cross-coupling reaction, which involves the coupling of aryl boronic acid with an organohalide, has proven to be a versatile tool in organic synthesis.^[1] Recent developments have led to catalysts based on sterically demanding, basic phosphanes allowing even the conversion of unreactive aryl chlorides.^[2] Nevertheless, these reactions still proceed very slowly at room temperature.^[3] As N-heterocyclic carbenes (NHC) are sometimes better ligands than phosphanes in homogeneous catalysis,^[4] they were also tested in cross-coupling chemistry.^[5–7] However, for the effective activation of aryl chlorides the known NHC-based catalysts require temperatures above 80 °C to yield reasonable activities. We now report on palladium(0) catalysts for the Suzuki cross-coupling at *ambient temperatures*.

Recently we established a synthetic procedure for homoleptic bis(NHC)-complexes of palladium(0) by ligand exchange in bis(tri-*ortho*-tolylphosphane)palladium(0) (**1a**).^[6] The catalytic activity of these complexes strongly depends on the steric bulk of the NHC ligand. 1,3-Bisadamantylimidazolin-2-ylidene (**2**), as one of the most bulky NHC ligands,^[8] represents a good candidate for palladium(0) catalysts of high activities in the Suzuki cross-coupling. However, even in presence of an excess of **2** only one phosphane ligand of **1a** was exchanged, which resulted in the formation of complex **3a** [Eq. (1)].

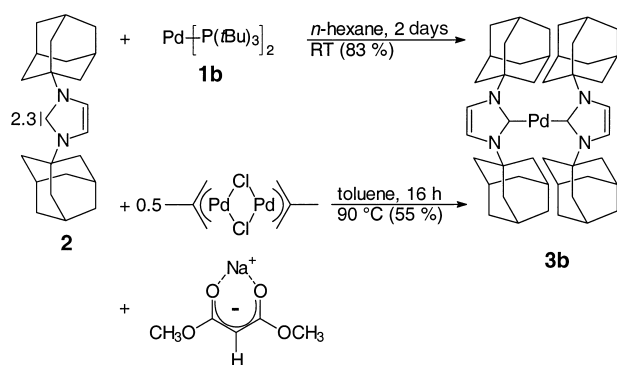


[*] Prof. Dr. W. A. Herrmann, Dipl.-Chem. C. W. K. Gstöttmayr, Dr. V. P. W. Böhm, Dr. E. Herdtweck, Dipl.-Chem. M. Grosche
 Anorganisch-chemisches Institut
 Technische Universität München
 Lichtenbergstrasse 4, 85747 Garching, Munich (Germany)
 Fax: (+49) 89-289-13473
 E-mail: lit@arthur.anorg.chemie.tu-muenchen.de

[**] N-Heterocyclic Carbenes, Part 32. This work was supported by the Deutsche Forschungsgemeinschaft (DFG), the Bayerischer Forschungsverbund Katalyse (FORKAT), and Bayer AG. We thank Dr. Öfele and Dr. Scholz for helpful discussion. Part 31 ref. [4c] (review in this issue).

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

There is only one other example of an isolated mixed NHC-phosphane complex of palladium(0) in the literature.^[9] Furthermore, **3a** is the first NHC-complex to catalyze the Suzuki cross-coupling of 4-chlorotoluene with phenylboronic acid at ambient temperature (20% conversion). Therefore, it was desirable to prepare the homoleptic palladium(0) complex **3b** as a potential catalyst. Screening various bis(phosphane)palladium(0) precursor complexes led to bis(tri-*tert*-butylphosphane)palladium(0) (**1b**) as the ideal starting material to form **3b** (83% yield, Scheme 1). Compound **3b** also resulted from the in situ reduction of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ in the presence of **2** at 90 °C (55% yield).^[10] This alternative procedure circumvents the use of the expensive starting material **1b**.^[11]



Scheme 1. Methods for the synthesis of **3b**.

Crystals suitable for X-ray diffraction studies were obtained from a diethyl ether solution at ambient temperature (Figure 1).^[12] The C-Pd-C angle is 180° and the NHC planes are twisted by 95.6(2)°. Therefore the palladium center is sterically encumbered.

Nevertheless, **3b** is a highly active catalyst in the Suzuki cross-coupling of aryl chlorides at room temperature (Table 1). For example, 4-chlorotoluene is coupled to phenyl

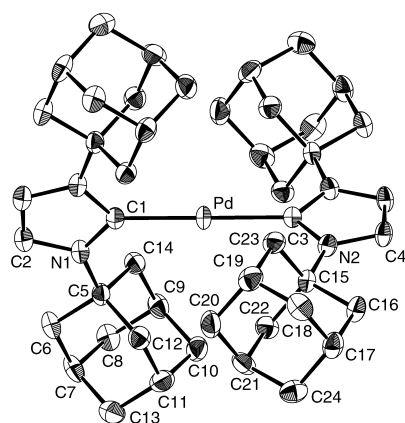


Figure 1. ORTEP^[13] drawing of the molecular structure of **3b** in the solid state. Thermal ellipsoids are set at the 50% probability level. Hydrogen atoms are omitted for clarity. Symmetry code: ($' \equiv -x, y, 0.5 - z$). Selected bond lengths [Å] and angles [°]: Pd-C1 2.076(5), Pd-C3 2.084(5), N1-C1 1.375(5), N1-C2 1.376(6), N1-C5 1.493(5), N2-C3 1.371(5), N2-C4 1.374(6), N2-C15 1.489(6), C2-C2' 1.322(7), C4-C4' 1.322(7); C1-Pd-C3 180.00, Pd-C1-N1 128.3(2), Pd-C3-N2 128.2(2), N1-C1-N1' 103.4(4), N2-C3-N2' 103.7(4).

Table 1. Suzuki cross-coupling of aryl chlorides with catalyst **3b**.^[a]

Entry	R ¹	R ²	<i>t</i>	[%] ^[b]
1	4-CH ₃	H	20 min	97 ^[c]
2	4-CH ₃	H	2 h	75
3	4-CH ₃	H	24 h	57 ^[d]
4	4-CH ₃	H	6 h ^[e]	> 99
5	4-OCH ₃	H	6 h ^[e]	> 99
6	4-CF ₃	H	2 h	95
7	4-CF ₃	H	6 h ^[e]	> 99
8	3-CH ₃	H	2 h	80
9	3-CH ₃	H	24 h	93
10	4-CF ₃	3-OCH ₃	24 h	97
11	4-COCH ₃	3-OCH ₃	24 h	95
12	4-CH ₃	3-OCH ₃	24 h	80

[a] 1.0 equivalent aryl chloride, 1.5 equivalents aryl boronic acid, 2.0 equivalents CsF, 3 mol % **3b**, 1,4-dioxane, RT unless otherwise stated. [b] GC-yield using diethyleneglycol-di-*n*-butyl ether as the internal standard. [c] At 80 °C. [d] At low catalyst loading with 0.1 mol % **3b**. [e] Reaction time not minimized.

boronic acid in the presence of 3 mol % of **3b** and two equivalents of CsF in 97% yield at 80 °C within 20 minutes (entry 1). At room temperature, the same result is obtained after 6 hours (entry 4). The starting turnover frequency (TOF)^[14] of 1100 [mol product mol Pd⁻¹ h⁻¹] in entry 1 and the turnover number (TON) of 573 [(mol product) (mol Pd)⁻¹ h⁻¹] (entry 3) are the highest reported to date for aryl chlorides under these conditions, thus illustrating the activity of catalyst **3b**. The use of 1,4-dioxane as well as two equivalents of CsF gives the best results. Other solvents such as toluene, diethyl ether, or THF give lower conversions. Regarding the salt additive, moderate conversions could still be detected with the use of Cs₂CO₃ while KF was less effective.

Sterically unhindered aryl chlorides can be converted with high to quantitative yields. The reaction time depends on the substituents in the *para* position of the aryl chloride and varies from 2–6 hours (Table 1, entries 4–7). Activated, electron-poor aryl chlorides react nearly quantitatively within 2 hours (Table 1, entry 6) whereas the deactivated ones need 6 hours for a similar conversion (entry 5). The substituents on the aryl boronic acid have an even greater effect on the reaction rates. While *meta* substitution can be compensated by electronically activated aryl chlorides (entries 10, 11), *ortho* substituents both in the aryl chlorides and in the boronic acids are less tolerable. Because of the bulky NHC ligands, sterically less demanding substrates react especially rapidly with the palladium center.

No induction period was observed in these catalytic reactions. However, since palladium black precipitates during the conversion, we cannot exclude that active clusters of the type [Pd_{*n*}(NHC)_{*m*}] (*n* > 0.5*m*) are formed.

In conclusion, we have developed a synthetic route to mixed and homoleptic palladium(0) complexes with sterically demanding N-heterocyclic carbene ligands. The homoleptic complex **3b** catalyzes the Suzuki cross-coupling and exhibits

the highest TON with aryl chlorides at room temperature reported so far. Various *para* and *meta* substituted substrates can be quantitatively converted within a few hours.

Experimental Section

3b: 1b (1000 mg, 1.81 mmol) was dissolved in *n*-hexane (30 mL). A solution of **2** (1400 mg, 4.16 mmol) in *n*-hexane (30 mL) was added. The mixture was stirred at ambient temperature for 24–48 h during which a yellow solid precipitated. After filtration and drying in vacuo the product was obtained as an analytically pure bright yellow solid. X-ray suitable crystals were obtained by recrystallization from diethyl ether. Yield: 1177 mg, 1.51 mmol, 83%; m.p. > 285 °C (decomp.); ¹H NMR (400 MHz, [D₈]toluene, 25 °C): δ = 1.47–1.80 (m, 24H, CH₂ of C₁₀H₁₅), 2.06–2.12 (m, 12H, CH of C₁₀H₁₅), 3.05 (s, 24H, CH₂ of C₁₀H₁₅), 6.69 (s, 4H, NCHCHN); ¹³C{¹H} NMR (100.5 MHz, [D₈]toluene, 25 °C): δ = 31.0, 36.8, 44.0 (C₁₀H₁₅), 57.2 (ipso-C of C₁₀H₁₅), 112.7 (NCHCHN), 191.8 (NCN); CI-MS: *m/z* (%): 778 (3) [*M*⁺], 336 (100) [NHC⁺], 281 (33), 207 (27), 203 (40); elemental analysis calcd (%) for C₄₆H₆₄N₄Pd (779.44): C 70.88, H 8.28, N 7.19; found: C 70.80, H 8.24, N 7.22.

Alternative synthesis: **2** (343 mg, 1.02 mmol), [(η³-C₃H₅)PdCl]₂ (100 mg, 0.254 mmol), and sodium dimethylmalonate (78 mg, 0.506 mmol) were suspended in toluene (30 mL) in a Schlenk tube. The stirred mixture was heated at 90 °C for 16 h after which the solution was brown. After cooling to room temperature, the mixture was filtered to remove some free palladium metal and the solution was concentrated. Crystallization at –50 °C yielded the product as bright yellow solid. Yield: 219 mg, 0.28 mmol, 55%.

Received: December 4, 2001 [Z18327]

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- [12] X-ray structure for **3b·H₂O**: bright yellow crystals, C₄₆H₆₄N₄OPd, crystal dimensions 0.38 × 0.32 × 0.24 mm; *M_r* = 797.45; monoclinic,

space group *C2/c* (no. 15), *a* = 23.436(2), *b* = 13.213(1), *c* = 12.999(1) Å, β = 104.645(9)°, *V* = 3894.5(6) Å³, *Z* = 4, λ(MoKα) = 0.71073 Å, μ = 0.518 mm^{–1}, ρ_{calcd} = 1.360 g cm^{–3}, *T* = 199(1) K, *F*(000) = 1696. Preliminary examination and data collection were carried out on a Stoe IPDS area detecting diffraction system at the window of a rotating anode (Nonius, FR591). The unit cell parameters were obtained by full-matrix least-squares refinement of 4977 reflections. A total number of 23284 reflections were collected (θ_{max}: 25.66°, exposure time: 300 s per image, 310 images, Δφ: 1.0°, dx: 70.0 mm). After merging (*R*_{int} = 0.0860) a sum of 3527 (all data) independent reflections remained and were used for all calculations. 2307 of them were observed data with *I* > 2σ(*I*). The structure was solved by direct methods (SIR-92)^[15] and refined by full-matrix least-squares on *F*² (SHELXL-97).^[16] All non-hydrogen atoms of the asymmetric unit were refined anisotropically. All hydrogen atoms were located in the difference Fourier map and refined with individual isotropic temperature parameters, except those located at the water oxygen. They were calculated in ideal positions (riding model). *R*1 = 0.0451 (observed data), *wR*2 = 0.1185 (all data), GOF = 0.934, 365 parameters, Δρ_{max/min} = 1.11/–0.97 e Å^{–3}. No correction for decay and absorption was applied. CCDC-175167 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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X-Ray Structural Characterization of a Monoorganotin Acid**

Jörg Janssen, Jörg Magull, and Herbert W. Roesky*

Dedicated to Sir John Meurig Thomas
on the occasion of his 70th birthday

The hydrolysis of monoorganotin trihalides has been a topic of interest in the chemistry of tin for a long time. Methylstannonic acid [Me(Sn(OH)O)] was first reported in 1922.^[1] It was proposed that monoorganotin acids exist either as cyclic trimers or as chainlike hydroxytin ethers; however, these structural elements could not be confirmed unambiguously.^[2] Functionalized organotin compounds are used in organic synthesis^[3] and catalytic reactions.^[4] Very recently Chandrasekhar et al. synthesized a hexaferrocene–tin–oxygen cluster containing a *cyclo*-tristannoxane-like structure by the reaction of *n*-butylstannonic acid with ferrocene monocarboxylic acid.^[5] Basic hydrolysis of diorganotin dihalides also yields tin–oxygen heterocycles,^[6,7] which show no additional sub-

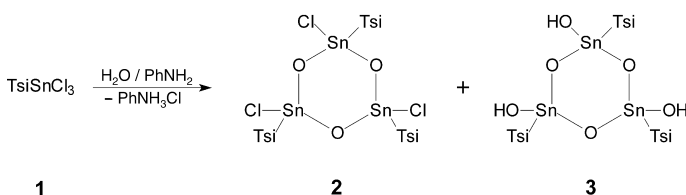
[*] Prof. Dr. H. W. Roesky, Dipl.-Chem. J. Janssen, Prof. Dr. J. Magull
Institut für Anorganische Chemie
Universität Göttingen
Tammannstrasse 4, 37077 Göttingen (Germany)
Fax: (+49) 551-39-3373
E-mail: hroesky@gwdg.de

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

stituents on the ring apart from the organic ligands. Further derivatization of these compounds is rather limited due to the strong tin–carbon bond.^[8]

A formal hydrolysis product of a monoorganotin trihalide was isolated for the first time in 1999: The reaction of TsiSnBr_3 ($\text{Tsi} = (\text{Me}_3\text{Si})_3\text{C}$) with Na_2O in liquid ammonia gave a product of the composition $[(\text{TsiSn})_4\text{O}_6]$ with a heteroadamantane-like structure. In this compound the tin atoms possess tetrahedral geometry.^[9] In contrast, basic hydrolysis of $n\text{BuSnCl}_3$ results in amorphous products, for which a polymeric structure of the composition $[(n\text{BuSn}(\text{OH})\text{O})_n]$ with only four-coordinate tin atoms was proposed.^[10] Mössbauer spectroscopic investigations by Davies et al. confirmed the tetrahedral coordination sphere of the tin atoms.^[11] Subsequent ^{119}Sn MAS NMR measurements, however, suggest only 80% of the tin atoms in $[n\text{BuSn}(\text{OH})\text{O}]$ display tetrahedral geometry and nearly 20% are five-coordinate.^[12]

Starting from TsiSnCl_3 (**1**),^[13] we attempted controlled hydrolysis reactions under mild conditions in the absence of alkali metal hydroxides, because the latter are known to lead to decomposition reactions at the silicon-substituted organic ligands.^[6] We used weakly basic aniline to trap the hydrochloric acid formed during the reaction, to avoid reactions between the nitrogen-containing base and the Lewis acidic tin atom. Surprisingly, the reaction of **1** with water yields the trimeric chloro compound $[(\text{TsiSn}(\text{O})\text{Cl})_3]$ (**2**) as the main product, whereas the expected stannonic acid $[(\text{TsiSn}(\text{OH})\text{O})_3]$ (**3**) is formed only as a by-product (Scheme 1).



Scheme 1. Reaction of **1** with H_2O in the presence of aniline. $\text{Tsi} = \text{C}(\text{SiMe}_3)_3$.

The tetrahedral coordination of the tin atoms in compounds **2** and **3** was confirmed by characteristic resonance signals in the ^{119}Sn NMR spectra (**2**: $\delta = -133, -141$; **3**: $\delta = -156$). These data are consistent with ^{119}Sn NMR resonances of tin compounds displaying similar coordination.^[14] Single crystals of the amine adduct of **3** were obtained from a solution of the crude product in a mixture of *n*-pentane and neopentylidimethylamine (4:1) and were characterized by X-ray crystallography.^[15, 16]

The reaction of **1** with water yields **3** in a yield of about 2%, which indicates that the $\text{Sn}–\text{Cl}$ bond in **2** is very stable towards hydrolysis. Compound **3** can be obtained in a 50% yield by treatment of **2** with LiOH in *n*-hexane under reflux [Eq. (1)].



NMR spectroscopic investigations of the compounds **2** and **3** indicate that the trifunctionalized *cyclo*-tristannoxanes exist as different conformers. The NMR spectra recorded for **2** show two resonance signals for each of the nuclei (^1H , ^{13}C , ^{29}Si ,

^{119}Sn). The ^1H NMR spectrum recorded at 80°C shows that **2** is stable to thermal-induced rearrangement reactions up to this temperature.

Compound **3**· $t\text{BuCH}_2\text{NMe}_2$ has an ideal chair conformation (Figure 1). The three organic ligands are bonded to the Sn_3O_3 heterocycle in equatorial positions. The three axial hydroxy groups show a *cis* arrangement. The amine is located

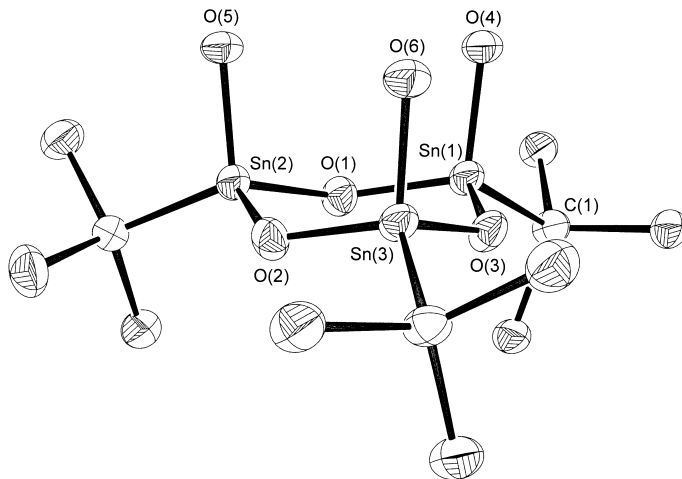


Figure 1. Molecular structure of **3**· $t\text{BuCH}_2\text{NMe}_2$ (ORTEP drawing,^[20] thermal ellipsoid plot (50% probability)). The hydrogen atoms, methyl groups, and the amine were omitted for clarity. Selected bond lengths [Å] and angles [°]: $\text{Sn}(1)–\text{O}(3)$ 1.965, $\text{Sn}(1)–\text{O}(4)$ 1.968, $\text{Sn}(1)–\text{C}(1)$ 2.156; $\text{O}(3)–\text{Sn}(1)–\text{O}(1)$ 104.99, $\text{O}(3)–\text{Sn}(1)–\text{O}(4)$ 106.06, $\text{O}(3)–\text{Sn}(1)–\text{C}(1)$ 114.4, $\text{O}(4)–\text{Sn}(1)–\text{C}(1)$ 110.5.

between two organic ligands (not shown). Interactions through hydrogen bonds between the amine $t\text{BuCH}_2\text{NMe}_2$ and **3** were not observed. Compounds **2** and **3** were compared by NMR spectroscopy. Unlike for **2** the NMR spectra for **3** show only one resonance signal for the relevant nuclei (^1H , ^{13}C , ^{29}Si , ^{119}Sn). The tin–oxygen bond lengths range from 1.958 to 1.970 Å within the six-membered ring of **3**· $t\text{BuCH}_2\text{NMe}_2$ and are comparable with those in known Sn_3O_3 heterocycles.^[6, 7] The distances between tin and the axially bonded oxygen atoms (1.968 to 1.977 Å) are in the same range as those in hydroxy-substituted tin–oxygen clusters.^[18] The tin–carbon bond lengths (2.145 to 2.156 Å) are similar to those in Tpsi-substituted tin compounds ($\text{Tpsi} = (\text{PhMe}_2\text{Si})_3\text{C}$).^[13a]

The presented synthesis and X-ray single-crystal structure analysis of the trimeric monoorganotin acid $[(\text{TsiSn}(\text{OH})\text{O})_3]$ (**3**) provides a clarification of the much-discussed structure of this type of compounds. The structure is consistent in terms of the tetrahedral coordination of the tin atoms with recent ^{119}Sn MAS NMR investigations of $[n\text{BuSn}(\text{OH})\text{O}]$. We eagerly anticipate a multitude of new products through the substitution of the oxygen-bonded hydrogen atoms.

Experimental Section

1: SnCl_4 (40.91 g, 157.0 mmol) was added slowly to Et_2O (1500 mL) at -78°C . A solution of $\text{TsiLi} \cdot 2\text{THF}$ (40.00 g, 104.5 mmol) in Et_2O (1500 mL) was added slowly under vigorous stirring to this freshly prepared suspension of $\text{SnCl}_4–\text{Et}_2\text{O}$ adduct. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred

for another 5 h. Finally all volatile components were removed in vacuo and the residue was dissolved in *n*-pentane (2000 mL). The insoluble components were filtered off and the colorless solution was concentrated under reduced pressure. Compound **1** crystallized as a colorless solid (43.42 g, 95.1 mmol, 91 %). The physical data of **1** are consistent with those reported by Eaborn et al.^[13a]

2: Compound **1** (35.00 g, 76.6 mmol) was dissolved in *n*-pentane (1000 mL), and water (8.70 g, 482.6 mmol) and aniline (25.83 g, 277.3 mmol) were added to this solution. The resulting reaction mixture was heated under reflux for 21 days. Subsequently, all volatile components were removed in vacuo, and the residue was dissolved in *n*-pentane (1000 mL). The resulting solution was filtered and the solution was concentrated continuously under an inert atmosphere. Compound **2** crystallized as large colorless crystals (23.14 g, 19.2 mmol, 75 %). M.p. 295–300 °C; ¹H NMR (C₆D₆, 300 K, 500 MHz): δ = 0.47 (s, 54H; (H₃C)₃Si[Sn(1,2)]), 0.50 (s, 27H; (H₃C)₃Si[Sn(3)]); ¹H NMR (C₆D₆, 353 K, 500 MHz): δ = 0.47 (s, 54H; (H₃C)₃Si[Sn(1,2)]), 0.50 (s, 27H; (H₃C)₃Si[Sn(3)]); ¹³C NMR (C₆D₆, 300 K, 125 MHz): δ = 5.32 (s; (H₃C)₃Si[Sn(3)]), 5.36 (s; (H₃C)₃Si[Sn(1,2)]), 26.71 (s; CSn(1,2)), 26.99 (s; CSn(3)); ²⁹Si NMR (C₆D₆, 300 K, 100 MHz): δ = 0.61 (s; SiSn(1,2)), ²J(²⁹Si, ¹¹⁹Sn) = 81.3 Hz, ²J(²⁹Si, ¹¹⁷Sn) = 77.8 Hz), 0.76 (s; SiSn(3)), ²J(²⁹Si, ¹¹⁹Sn) = 81.3 Hz, ²J(²⁹Si, ¹¹⁷Sn) = 77.8 Hz); ¹¹⁹Sn NMR (C₆D₆, 300 K, 186 MHz): δ = −141.0 (Sn(3)), ²J(¹¹⁷Sn, ¹¹⁹Sn) = 829 Hz), −133.0 (Sn(1,2)), ²J(¹¹⁷Sn, ¹¹⁹Sn) = 822 Hz); elemental analysis calcd for C₃₀H₈₁Cl₃O₃Si₉Sn₃ (1205.16 g mol^{−1}) (%): C 29.90, H 6.77, Cl 8.83; found: C 30.56, H 6.87, Cl 9.19; IR (CCl₄): ν̄ = 599 w, 619 w, 661 w, 680 w, 756 vs, 768 vs, 856 vs, 1023 w, 1096 w, 1256 vs, 1269 vs, 1867 w, 1934 w, 2902 s, 2951 s, 2981 s cm^{−1}; MS (70 eV): *m/z*: 1205 [*M*⁺], 1190 [*M*⁺ − Me], 944 [*M*⁺ − TMS₃C − 2 Me].

3: A solution of **2** (400.0 mg, 0.33 mmol) in *n*-hexane (50 mL) was added to a suspension of LiOH (50.0 mg, 1.98 mmol) in *n*-hexane (50 mL). The reaction mixture was heated under reflux for 28 days. After the reaction was complete, all volatile components were removed in vacuo. The colorless residue was extracted for 5 h with *n*-pentane (75 mL). Finally the insoluble solid was filtered off and the resulting colorless solution was concentrated under reduced pressure. Fractional crystallization at −26 °C yielded **3** as a colorless solid (195 mg, 0.17 mmol, 50 %). M.p. 145–147 °C; ¹H NMR (C₆D₆, 300 K, 500 MHz): δ = 0.28 (s, 81H; (H₃C)₃Si); ¹³C NMR (C₆D₆, 300 K, 125 MHz): δ = 5.19 (s; (H₃C)₃Si), 26.55 (s; CSn); ²⁹Si NMR (C₆D₆, 300 K, 100 MHz): δ = 0.26 (s, ²J(²⁹Si, ¹¹⁹Sn) = 74.5, ²J(²⁹Si, ¹¹⁷Sn) = 70.4 Hz); ¹¹⁹Sn NMR (C₆D₆, 300 K, 186 MHz): δ = −156.3 (s, ²J(¹¹⁷Sn, ¹¹⁹Sn) = 719 Hz); elemental analysis calcd for C₃₀H₈₄O₆Si₉Sn₃ (1149.83 g mol^{−1}) (%): C 31.34, H 7.36; found: C 30.92, H 7.41; IR (CCl₄): ν̄ = 629 w, 662 w, 682 w, 981 w, 1013 s, 1098 s, 1550 vs, 1734 w, 1867 w, 1936 w, 2905 s, 2957 s, 2986 s, 3588 w cm^{−1}.

Received: October 31, 2001 [Z18139]

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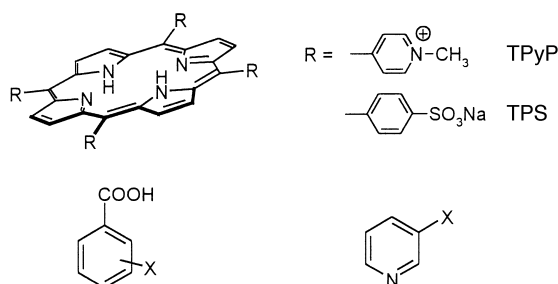
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Additivity and Quantification of Dispersive Interactions—from Cyclopropyl to Nitro Groups: Measurements on Porphyrin Derivatives**

Tianjun Liu and Hans-Jörg Schneider*

The investigation of supramolecular complexes opens up pathways to the identification of noncovalent interactions, such interactions are also of importance for biology and materials science. One example is the discovery of high-order effects in the form of cation– π interactions in organic host–guest complexes.^[1] Dispersive Van der Waals interactions have hitherto defied a corresponding empirically based characterization. At the same time their theoretical calculation encounters considerable problems largely because of the need to consider polarization.^[2] We report here the systematic analysis of host–guest complexes, with porphyrin derivatives in water as host molecules, which for the first time allows an unambiguous identification of dispersive interactions and provides generally applicable energy increments.

Porphyrins are made water soluble by the insertion of pyridinium or sulfonic acid moieties (TPyP or TPS, Scheme 1) into the *meso* positions, and are then highly suitable for the analysis of noncovalent interactions.^[3] They show an intense



Scheme 1. Structures of porphyrins TPyP and TPS and the general formulae of the benzoic acids B and pyridines py used as guests.

absorption band at about 400 nm (Soret band) which can be readily used as a probe for the UV spectroscopic determination of equilibrium constants. Above all, however, because of their large surface, porphyrins are relatively tolerant of the necessary geometric adaptation between host and guest molecule, as long as the guest is sufficiently small. Moreover, noncovalent interactions with porphyrins and related compounds are of considerable importance in biological systems.^[4]

The identification of noncovalent interactions in supramolecular structures is of limited value if the interactions

cannot be energetically quantified in an adequate number of systems.^[5] We have determined the complexation constant *K* for a number of guests (Tables 1 and 2 and Table I of the Supporting Information) with the porphyrins TPyP and TPS as host molecules by the previously described methodology.^[6] In the selection of substrates attention was given to a different combination of components, for example, benzene rings,

Table 1. Substituents X of the benzoic acid derivatives **B1**–**B29** the complexation of which was investigated with the porphyrin derivatives TPyP and TPS.

X	X	X
B1 H	B11 4-I	B21 3-NO ₂
B2 4-CH ₃	B12 4-OCH ₃	B22 4-NO ₂
B3 3,5-dimethyl	B13 4-COOCH ₃	B23 3,5-dinitro
B4 4-CH(CH ₃) ₂	B14 4-COCH ₃	B24 3,4-dinitro
B5 3-CH ₂ Cl	B15 3,5-dimethoxy	B25 3,4-difluoro
B6 4-CH ₂ Cl	B16 4-NH ₂	B26 3,5-difluoro
B7 4-CH=CH ₂	B17 4-SCH ₃	B27 3,4-dichloro
B8 4-F	B18 4-CN	B28 3,5-dichloro
B9 4-Cl	B19 4-CONH ₂	B29 3,5-dibromo
B10 4-Br	B20 2-NO ₂	

Table 2. Further compounds, the complexation of which was investigated with the porphyrin derivatives TPyP and TPS.

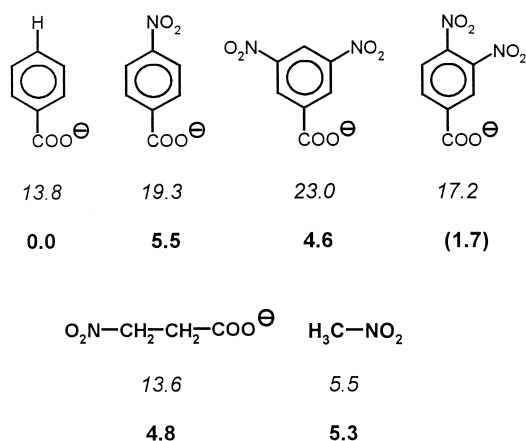
X	
Pyridine	Peptides and others
py1 H	Pp3 Gly-Gly-Gly-OH
py2 3-Br	Pp4 Gly-Gly-Gly-Gly-OH
py3 3-CN	Pp5 Gly-Gly-Gly-Gly-Gly-OH
py4 3-OCH ₃	M1 HC≡C(CH ₂) ₂ COOH
py5 3-I	M2 HOCH ₂ C≡CC=CCH ₂ OH
	M3 CH ₂ =CHCOOH
	M4 CH ₃ CH=CHCOOH
X-CH ₂ -CH ₂ -COOH	M5 cyclopropyl-COOH
Pr1 H	M6 (cyclopropyl) ₂ CHOH
Pr2 Br	M7 C ₆ H ₅ CH=CHCOOH
Pr3 I	M8 CH ₃ NO ₂
Pr4 NO ₂	M9 NaNO ₃
	M10 NaI

carboxyl, and nitro groups. Our investigations confirm an astonishing additivity in the complexation energy contributions of the individual groups. This trend is illustrated in Scheme 2 for the nitro compounds investigated: a constant value of $\Delta\Delta G = 5 \text{ kJ mol}^{-1}$ can be assigned to the ion-pair bonding between the carboxyl group and the positively charged porphyrin, as was found in numerous complexes with the ion strengths used here.^[7] A $\Delta\Delta G$ value of about 8 kJ mol^{-1} is assigned to the bonding contribution of the benzene unit (see Table 3) from previous^[6] and more recent measurements (e.g. comparison of benzoic acid **B1** and propionic acid **Pr1**, Table I of the Supporting Information). The $\Delta\Delta G$ value for the ion-pair bond and for benzene confirm the new data: a constant contribution for the nitro group of $\Delta\Delta G = 5 \text{ kJ mol}^{-1}$ is derived from the *K* values measured for three nitrobenzoic acids; this even applies, within the error limits, to aliphatic guest molecules such as nitromethane **M8** or 3-nitropropionic acid **Pr4**. As with free energy relationships, for instance of the Hammett correlation type, deviations from additive behavior normally arise if substituents are

[*] Prof. Dr. H.-J. Schneider, Dr. T. Liu
FR Organische Chemie der Universität des Saarlandes
and Institut für Neue Materialien
66041 Saarbrücken (Germany)
Fax: (+49) 681-302-4105
E-mail: ch12hs@rz.uni-sb.de

[**] This work was supported by the DFG. T.L. thanks the Alexander von Humboldt Stiftung for a stipend.

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



Scheme 2. Experimental bond energies ΔG [kJ mol⁻¹] (italics) with TPyP as host compound (in water at 25 °C) and bond energy increments $\Delta\Delta G$ for the nitro group (bold); $\Delta\Delta G$ is the difference between the ΔG values of the compounds with R = NO₂ and R = H.

located in a vicinal position (example: 2-nitrobenzoic acid **B20** and 3,4-dinitrobenzoic acid **B24**). In all other cases the $\Delta\Delta G$ contributions of the substituents to the Gibbs complexation energy ΔG were additive. The additivity and applicability of the increments are illustrated in Figure 1 by a comparison of calculated and measured ΔG values.

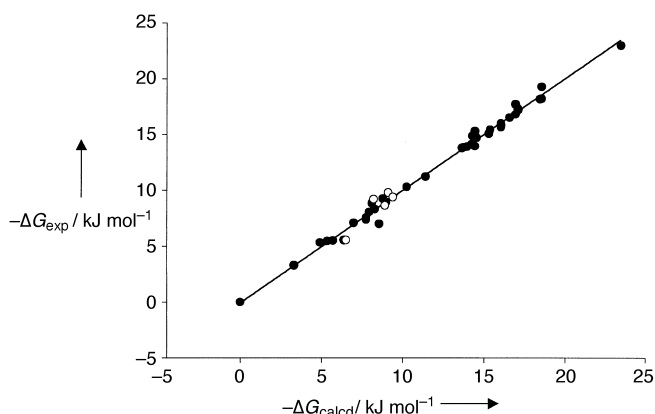


Figure 1. Calculated ΔG against measured Gibbs complexation energies. Calculation with increments from Table 3, correlation line with slope $m = 1.007$, correlation coefficient $r = 0.996$; ●: complexes with TPyP, ○: complexes with TPS.

On the basis of measured data, bond energy increments $\Delta\Delta G$ can be assigned to numerous groups (Table 3). The increase in interaction with increasing polarizability, such as within the halogens, demonstrates that these are dispersive interactions. The π electrons also produce an additive bonding contribution.^[6] It is interesting that we were able to observe—considerable—noncovalent interactions of the cyclopropane rings, which is in agreement with bonding model for the three-membered ring. Moreover, the contributions of the amide and, especially, of the nitro function are also notably large. That this result is not a consequence of donor–acceptor or electrostatic interactions is confirmed in that the same ΔG values are obtained with anionic host compounds as with cationic host compounds (TPS, TPyP); the influence of salt bridges must be taken into account in the calculation (Table II

Table 3. Bond energy increments $\Delta\Delta G$ [kJ mol⁻¹] for different substituents X.^[a]

X	$\Delta\Delta G$	$n^{[b]}$	X	$\Delta\Delta G$	$n^{[b]}$
CH ₃	< 0.5	4	I	2.95	3
CH(CH ₃) ₂	0.6	1	NH ₂	0.9	1
CH=CH ₂	2.4	6	OCH ₃	1.75	3
C≡C-	2.6	1	COOCH ₃	3.1	1
cyclopropyl	1.65	2	COCH ₃	3.15	1
phenyl	8.3	6	SCH ₃	2.8	1
pyridyl	6.4	5	CN	2.6	2
F	0.3	3	NO ₂	4.95	5
Cl	1.65	5	CONH ₂	2.85	5
Br	2.4	4			

[a] $\Delta\Delta G$ calculated from association constants with tetrapyrrolylporphyrin TPyP (in water, 298 K, pH 7.00 ± 0.01, phosphate buffer, ion strength $I = 0.05$ M, unless otherwise stated); scatter of the $\Delta\Delta G$ values for different compounds: ± 0.25 kJ mol⁻¹ (± 0.35 kJ mol⁻¹ for R = I, COCH₃). [b] n : number of the compounds used in each case for the $\Delta\Delta G$ calculation.

of the Supporting Information). Equally the analogous and always affinity-enhancing effect of, for example, nitro, amino, and methoxy groups in benzoic acids is only compatible with a dispersive mechanism. Conjugative interactions in substituted aromatic guest compounds clearly play no significant role since an almost constant $\Delta\Delta G$ value was obtained for the nitro substituents in mono- and disubstituted aromatic and aliphatic compounds.

A considerable problem in the analysis of noncovalent interactions in water is the differentiation of solvophobic and lipophilic effects. The negligibly small contributions of the methyl groups already show that the observed associations arise only to a small measure from the hydrophobic interactions. This proposal is confirmed by the comparison of the association energies of cyclohexanoic acid and benzoic acid **B1**: although the hydrophobic surfaces of both six-membered rings are of approximately the same size cyclohexanoic acid exhibits only the value $\Delta G = 5$ kJ mol⁻¹ typical for ion-pair bonding, whereas as a result of the six- π -electron system the value for benzoic acid is $\Delta G = 14$ kJ mol⁻¹.^[6] Moreover, the measured association constants (Table I of the Supporting Information) do not correlate at all with the lipophilic nature of the substrates used or with the corresponding substituent Hansch effects.^[8]

The energy increments listed in Table 3 need not only be used for interactions with porphyrins. As long as an adequate contact exists between the surfaces of the substituents and those of the host molecule a general applicability can be presumed. As with the substituent constants in the Hammett relationship, the $\Delta\Delta G$ values listed are relative quantities which, for example, in complexes with smaller host compounds or with an increase in the ionic strength of the aqueous solution decrease by a constant factor (scaling similar to the reaction constant ρ in free energy relationships). Earlier we described how the complexation energy increases considerably at very low buffer concentrations,^[9] more than can be explained with the salt effects expected from Coulombic interactions.

The addition of organic solvents in aqueous medium leads, in many host–guest complexes, to a smaller association

energy by reduction not only of the hydrophobic interaction, but also of other interactions. Diederich et al.^[10] have already pointed out that, because of its extremely low polarizability, water is an excellent medium for the maximization of many interactions.

The association constant of the complex from TPyP and 3,5-dinitrobenzoic acid **B23** was determined relative to the ethanol content of an ethanol–water mixture. Figure 2 shows a linear correlation of the logarithm of the association

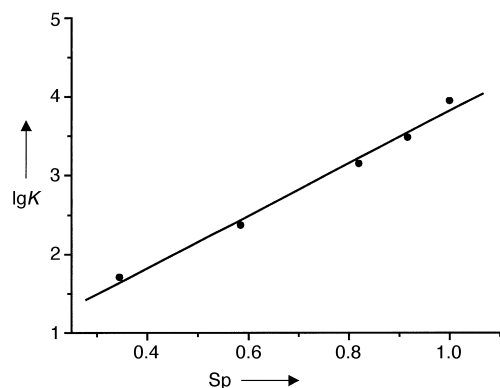


Figure 2. Solvent effect: logarithm of the association constant, $\lg K$, for 3,5-dinitrobenzoic acid and TPyP against the solvophobic parameters Sp of ethanol–water mixtures; ●: experimental data; correlation line slope $m = 3.33$, correlation coefficient $r = 0.995$.

constant $\lg K$ with the solvophobicity parameter (Sp)^[11] ($r = 0.995$). A linear correlation with almost an identical correlation was also found between $\lg K$ and solvent polarity E_T ($R = 0.999$), or simply the alcohol volume fraction^[12] (Figures 1 and 2 of the Supporting Information). The slope in the correlation line $\lg K$ against Sp is at $m = 3.33$ significantly lower than in host–guest complexes with cyclodextrins as host compounds ($m = 7.0$).^[13] The latter are typically stabilized by hydrophobic effects.

In conclusion we have, for the first time, successfully achieved both the mechanistic differentiation of dispersive interactions and the quantification of individual energy contributions to these interactions in a targeted investigation of organic host–guest complexes. This type of intermolecular force plays a large role in the folding of proteins, their interactions with many ligands, and in stacking interactions between nucleobases. The latter are now recognized as the dominating factor in the formation of the double helix.^[14] The

contributions now available for of individual substituents, for example the amino group, are of particular interest because in folded nucleic acids, exocyclic groups lie over nucleobases more frequently than the π systems themselves.^[15] The rational development of new host–guest systems as well as new materials and crystal engineering strategies can benefit in that energy contributions to dispersive interactions can now be attributed to individual groups. The data obtained show that the preparatively easy introduction of, for example, two nitro groups can lead to the same intermolecular forces as that of a single phenyl group. Noteworthy is that the interactions analyzed here are strongest not in organic solvents, but, in water, in the gas state, and above all in the solid state.

Received: 20 November 2001 [Z 18251]

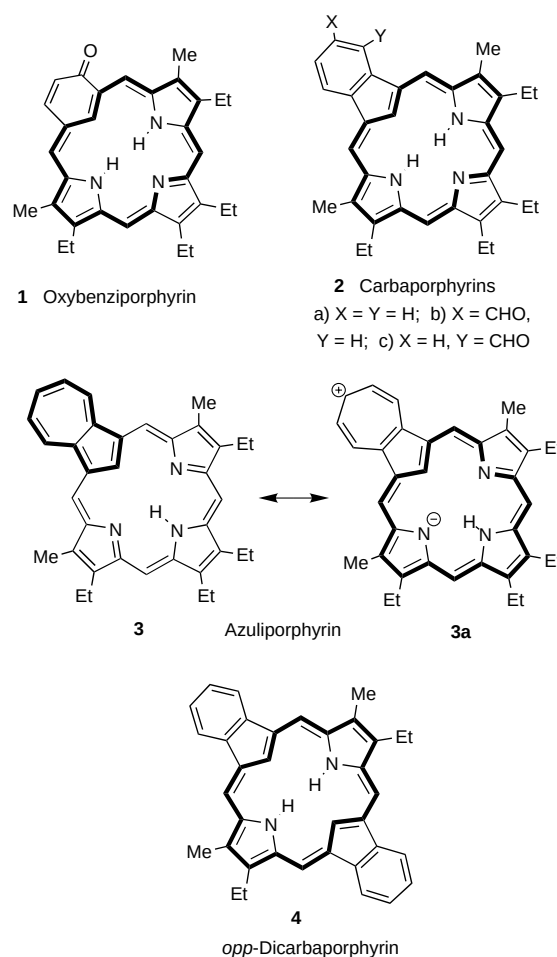
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An Azulene Analogue of the Tripyrranes and Carbaporphyrinoids Therefrom**

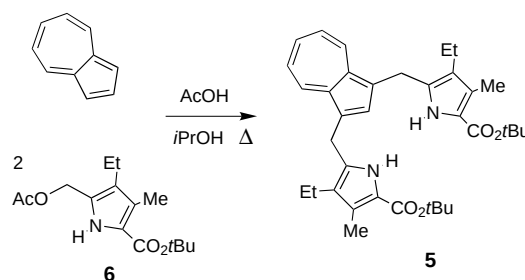
Shelley R. Graham, Denise A. Colby, and Timothy D. Lash*

The “3+1” approach to porphyrinoid systems^[2] provides an extraordinarily versatile methodology for the synthesis of novel conjugated structures related to the porphyrins.^[1–5] The method relies upon the ready availability of tripyrranes^[2, 6] and their ability to condense with various dialdehydes to give macrocycles that are built up from three pyrrole rings and a fourth, potentially dissimilar, subunit. This methodology has allowed the synthesis of carbaporphyrinoids with benzene (for example, **1**),^[1, 5, 7] indene (for example, **2**),^[8] azulene (for example, **3**),^[9] or related subunits,^[10] as components of the conjugated macrocycle. The methodology is less well suited to the synthesis of more functionalized macrocycles, because of the lack of availability of suitable precursors. Synthesis of an aromatic *opp*-dicarbaporphyrin **4** by the condensation of 1,3-indanedialdehyde with 3,4-diethylpyrrole has been reported,^[11] but this is a special case and does not provide the basis for synthesis of related macrocycles. There is currently a great deal of interest in the synthesis of modified porphyrinoids of this type,^[3, 4] which include the related doubly N-confused porphyrins,^[12] but rational approaches for the synthesis of highly modified porphyrinoid systems remain to be developed. We now report the synthesis of an azulene analogue of the tripyrranes and its utility in the synthesis of novel porphyrinoid systems.

Azuliporphyrin (**3**) was prepared in good yields by condensing 1,3-azulenedicarbaldehyde with a tripyrrane under standard “3+1” conditions.^[9] The macrocycle is cross-conjugated but nonetheless possesses a weak diatropic ring current as demonstrated by ¹H NMR spectroscopy, caused by zwitterionic resonance contributors, such as **3a**.^[9] These aromatic characteristics dominate in the protonated species, in which porphyrinoid aromaticity is no longer undermined by charge separation.^[9] Interestingly, oxidative rearrangements have been reported, in which ring contraction takes place to afford the benzocarbaporphyrins **2a–c**.^[13] In our studies on the azuliporphyrins, we are investigating alternative routes to azulene-containing macrocycles. Azulene favors electrophilic substitution at the 1 and 3 positions, which are analogous to the α -positions on the pyrrole nucleus, and we speculated that



this characteristic would allow the synthesis of novel tripyrrane analogues such as **5** (Scheme 1). This type of “carbatrityrrane” could act as a precursor to a series of porphyrin analogues with two modified subunits.



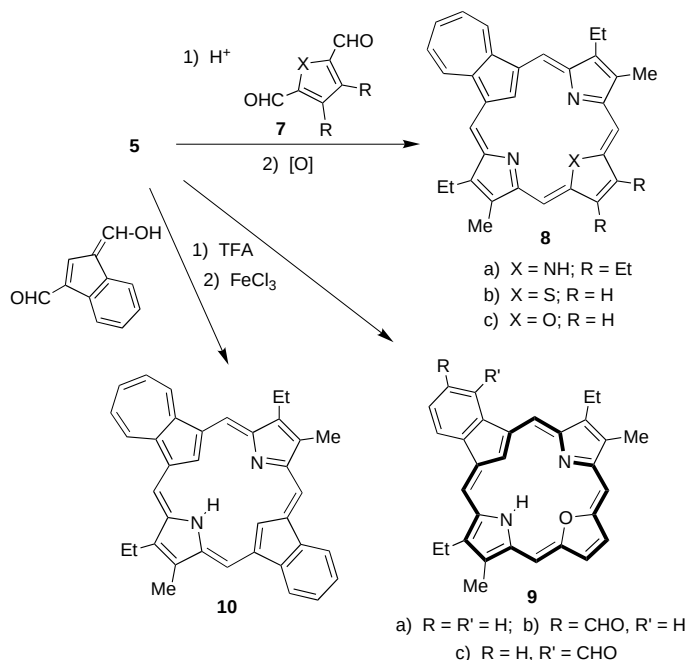
Scheme 1. Synthesis of an azulitripyrrane **5**.

The synthesis of carbatrityrrane **5** turned out to be remarkably straightforward. Condensation of azulene with two equivalents of acetoxymethylpyrrole **6** in refluxing acetic acid/isopropyl alcohol afforded the tripyrrane analogue in 59% yield, after column chromatography and recrystallization from toluene (Scheme 1). The system is stable compared with tripyrrolic tripyrranes and the simplicity of the synthesis may allow the preparation of many new macrocycles.

[*] Prof. Dr. T. D. Lash, S. R. Graham, D. A. Colby
Department of Chemistry
Illinois State University
Normal, Illinois 61790-4160 (USA)
Fax: (+1) 309-438-5538
E-mail: tdlash@ilstu.edu

[**] Conjugated Macrocycles Related to the Porphyrins, Part 19. This work was supported by the National Science Foundation under Grant Nos. CHE-9732054 and CHE-0134472. Mass spectral determinations were made at the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029). Elemental analyses were obtained from the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois. Part 18: ref. [1].

Tripyrrane **5** was treated with trifluoroacetic acid (TFA) to cleave the *tert*-butyl ester protective groups, and the resulting solution diluted with dichloromethane, treated with pyrrolealdehyde **7a**, and oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give azuliporphyrin **8a** in 25 % yield (Scheme 2). This method is a “back-to-front” synthesis



Scheme 2. “3+1” Syntheses of azuliporphyrin analogues.

of the azuliporphyrin system, and demonstrates the viability of this strategy. The resulting porphyrinoid **8a** only differs from **3** in the placement of the peripheral alkyl substituents and has very similar properties to the original porphyrinoid **3**.

Under the same conditions, **5** was condensed with 2,5-thiophenedicarbaldehyde (**7b**) to give the related thiaazuliporphyrin **8b** in 33 % yield. This system also shows borderline aromatic properties and the UV/Vis spectrum in 5 % Et_3N/CH_2Cl_2 had several moderate bands in the Soret band region at 372, 384, 448, and 477 nm, together with broad absorption bands between 500 and 800 nm that resemble the spectra of **3**.^[9] Both the UV/Vis and ^1H NMR spectra for the protonated system show the manifestation of fully aromatic character (for example, the emergence of a Soret band at 468 nm and the presence of a diatropic ring current) as reported for **3**. Reaction of **5** with furandialdehyde **7c**, however, did not give the expected oxazuliporphyrin **8c**, but instead a mixture of three oxacarbazoporphyrins **9a–c** was isolated in a combined yield of 15 % (Scheme 2). These compounds were presumably formed by ring contraction of the seven-membered ring, analogous to that of the parent system.^[13] All three of the products, which represent a new macrocyclic system, were shown to be fully aromatic porphyrinoids by UV/Vis and NMR spectroscopy. The ^1H NMR spectra show the resonance signals of the internal CH units between $\delta = -6$ and -7 , while the signals from the external *meso*-protons were observed downfield, between $\delta = 9.8$ and 10.9.

The success of these studies encouraged us to consider the first rational synthesis of a dicarbaporphyrin. Treatment of **5** with TFA, followed by reaction with diformylindene in CH_2Cl_2 and oxidation with $FeCl_3$, afforded the carbaazuliporphyrin **10** in 9.4 % yield (Scheme 2). This new dicarbaporphyrinoid also appears to be weakly diatropic by ^1H NMR spectroscopy (Figure 1). The internal protons gave rise to three singlets in the upfield region at $\delta = 2.0$, 1.3, and 0.5, while the *meso*-protons appeared as two broadened singlets downfield between 8.4 and 8.7 ppm. The UV/Vis spectrum of **10** in chloroform has two broad bands at 494 and 675 nm (Figure 2). These results demonstrate that the system is nonaromatic, although dipolar contributors do allow for a weak diatropic ring current. Addition of trace amounts of TFA to the NMR solution gave rise to a monocation **11** and this shows a pronounced ring current with three upfield resonances at $\delta = -3.68$ (1 H), -2.37 (1 H), and -1.16 (2 H). The signals arising from the *meso*-protons of **11** sharpened considerably and shifted downfield to $\delta = 8.87$ and 9.43. Further addition of TFA led to C protonation on the interior indene carbon, to afford the dication **12** (Scheme 3). C protonation of this type has previously been reported for mono- and dicarbaporphyrin systems,^[8, 11] as well as for carbasaporphyrins.^[10d] However, it is notable that both **11** and **12** appear to be stabilized by charge delocalization caused by dipolar canonical forms such as **11a** and **12a**. In **12**, the 18- π -electron delocalization pathway is redirected through the fused benzene ring which causes the resonance signals from the benzo moieties to shift downfield from $\delta = 7.76$ and 8.25 in **11**, to $\delta = 8.40$ and 9.26 in **12**. The protons of the internal methylene group of **12** resonate at $\delta = -0.90$, while the resonance signal arising from the inner azulene proton is observed at $\delta = 1.49$ and the signals of the NH protons are evident at $\delta = 4.33$ ppm. In the UV/Vis spectrum, the addition of TFA to dilute solutions failed to show the formation of an intermediary monocationic species and the free-base spectrum evolved directly into the spectrum for the doubly-protonated species. Dication **12** gave a strong Soret-like band at 481 nm and weaker bands at 529, 623, and 670 nm (Figure 2).

In conclusion, we have demonstrated that an azulene-containing analogue of the tripyrranes can easily be synthesized by the electrophilic substitution of azulene. The synthesis of several new macrocyclic systems from this key intermediate demonstrates that this back-to-front “3+1” methodology can be utilized to construct porphyrinoids with two modified subunits. In addition, the method provides a convenient synthetic entry to dicarbaporphyrinoid macrocycles.

Experimental Section

5: Azulene (0.438 g) and **6** (2.140 g) were stirred and heated under reflux in acetic acid (10 mL) and 2-propanol (50 mL) under a nitrogen atmosphere for 16 h. The solvent was removed under reduced pressure and the residue chromatographed on a silica column eluting with CH_2Cl_2 /hexanes (60/40). A major blue band was collected, the solvent evaporated, and the residue recrystallized from toluene to give the carbatrityrrane (1.027 g; 59 %) as a pale blue powder. Selected physical and spectroscopic data for **5**: m.p. 150 °C (dec.), ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (6 H, t, $J = 7.4$ Hz), 1.47

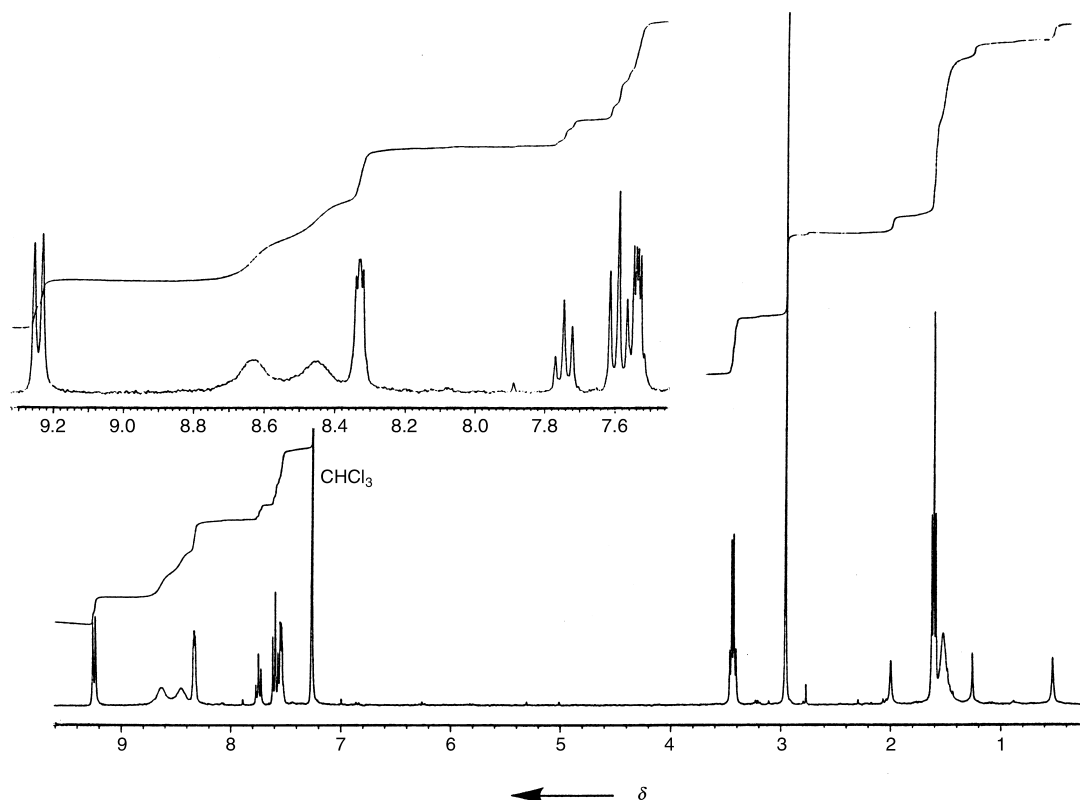


Figure 1. 400 MHz ^1H NMR spectrum of **10** in CDCl_3 .

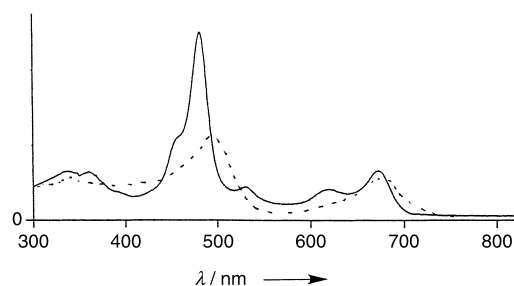
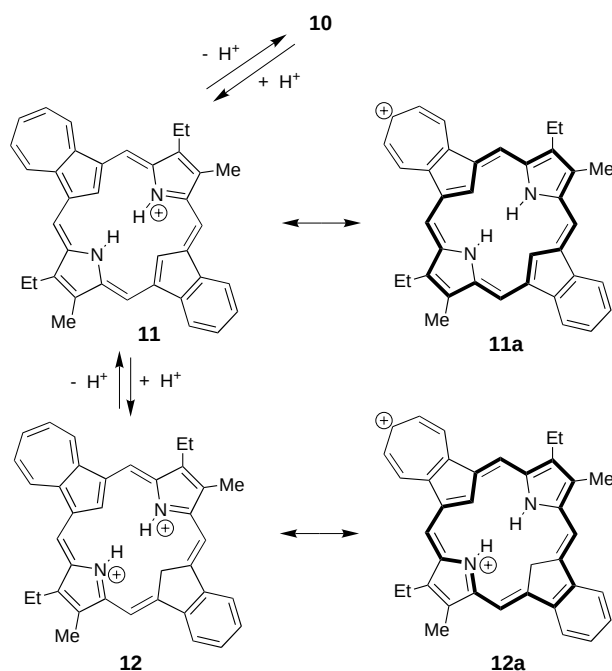


Figure 2. UV/Vis spectra of **10** in chloroform (---, free base) and 1% TFA/ CHCl_3 (—, dication **12**).

(18H, s), 2.26 (6H, s), 2.48 (4H, q, $J = 7.4$ Hz), 4.31 (4H, s), 7.08 (1H, t, $J = 9.8$ Hz), 7.49 (1H, s), 7.56 (2H, t, $J = 9.8$ Hz), 8.11 (2H, br s), 8.18 (2H, d, $J = 10$ Hz); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 10.74$, 15.74, 17.56, 24.31, 28.69, 80.23, 118.65, 122.42, 123.43, 124.66, 125.98, 131.59, 133.69, 137.04, 138.42, 138.67, 161.55; HRMS (EI): calculated for $\text{C}_{36}\text{H}_{46}\text{N}_2\text{O}_4$: m/z 570.3458; found: 570.3458; elemental analysis (%) calcd for $\text{C}_{36}\text{H}_{46}\text{N}_2\text{O}_4$: C 75.76, H 8.12, N 4.91; found: C 75.30, H 8.16, N 4.60.

10: Di-*tert*-butyl carbatripyrrane **5** (230 mg) was stirred with TFA (1 mL) under a nitrogen atmosphere for 10 min. Dichloromethane (49 mL) was added, followed immediately by addition of 1,3-diformylindene (72 mg) and the mixture was stirred under nitrogen for another 2 h. The mixture was diluted to 150 mL with chloroform and shaken with an aqueous ferric chloride solution (0.1%, 200 mL) for 5 min. The organic phase was separated and washed with water, 5% sodium bicarbonate solution, and water again. The combined organic solutions were dried over sodium sulfate and evaporated under reduced pressure. The brown residue was purified on a grade III alumina column eluting with 1% triethylamine/chloroform. The green product fraction was further purified on silica by flash chromatography eluting with 1% triethylamine/chloroform. A green fraction was collected, evaporated to dryness, and the residue recrystallized from chloroform/hexanes to give the dicarba porphyrinoid (19.1 mg, 9.4%)

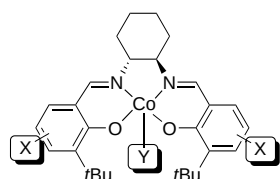


Scheme 3. Protonation of benzocarbazuliporphyrin **11**.

as dark green crystals. Selected physical and spectroscopic data for **10**: m.p. 228–230 °C (dec.), UV/Vis (CHCl_3): λ_{max} ($\log \epsilon$) = 494 (4.74), 675 nm (4.44); UV/Vis (1% TFA/ CHCl_3): λ_{max} ($\log \epsilon$) = 481 (5.08), 529 (4.32), 623 (4.29), 670 nm (4.59); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.52$ (1H, s), 1.25 (1H, s), 1.60 (6H, t, $J = 7.4$ Hz), 1.99 (1H, s), 2.95 (6H, s), 3.43 (4H, q, $J = 7.4$ Hz), 7.51–7.55 (2H, m), 7.59 (2H, t, $J = 9.6$ Hz), 7.75 (1H, t, $J = 9.6$ Hz), 8.31–8.35 (2H, m), 8.45 (2H, br s), 8.64 (2H, br s), 9.24 (2H, d, $J = 9.6$ Hz);

cyclic framework. In addition, the local C_2 symmetry in the individual salen units allowed oligomerization to be effected simply by condensation of dialdehyde and 1,2-diamine in a 1:1 molar ratio. However, problems tied to the structure and synthesis of **1** detract from the utility of this catalyst system. Specifically, installation of the chlorine substituents in the α and α' positions of the linker units requires harsh conditions and proceeds in only moderate yield, with the requisite purification limiting mass throughput. Once installed, the chlorine substituents activate the adjacent carbonyl groups and render the oligomer sensitive to decomposition under the conditions of epoxide ring-opening. Finally, a statistical mixture of diastereomeric linker units was generated and introduced into the oligomer; the synthesis of **1** could thereby produce in excess of 1000 discrete compounds considering all possible diastereomers of the observed ring sizes.^[3] This presents an obvious barrier to understanding how the cyclic oligomeric salen framework imparts both high reactivity and enantioselectivity in epoxide ring-opening reactions.

The issues outlined above are all tied to the presence of the chlorine substituents in the linker unit of **1** and would be circumvented if a simpler pimelate-linked system derived from **2** were employed instead.^[4] The impetus for introducing the chlorine substituents in the first place arose from an empirical screen of monomeric model systems. This study revealed that electronic tuning of carboxylate-substituted



Scheme 1. Sites for electronic tuning of the [(salen)Co] catalysts: the ancillary ligand(s) that do not participate directly in catalysis (Scheme 1). Only recently

has it become apparent that this might be a viable option for optimization of salen-based catalysts for epoxide ring-opening.^[5] Clearly, it suggests a more straightforward strategy for tuning the electronic environment of the metal center in the oligomeric complexes.

Pimelate-linked oligomeric [(salen)Co^{II}] complex (**2**) was prepared and oxidized with air in the presence of a variety of Brønsted acids (HX) to provide the corresponding [(salen)-Co^{III}(X)] oligomers. These complexes were evaluated for their ability to catalyze the asymmetric hydrolysis of cyclohexene oxide. Whereas oxidation with air/*p*-toluenesulfonic acid led to a catalyst that was less effective than **1**, catalysts generated by oxidation with camphorsulfonic acid (**3**, CSA = 10-camphorsulfonate) and 3-nitrobenzenesulfonic acid (**4**, NBS = 3-nitrobenzenesulfonate) displayed comparable reactivity and slightly improved selectivity relative to **1** (Table 1, entries 1 versus 3 and 5).^[6, 7] Longer reaction times and decreased reaction temperature were required to obtain highly enantioenriched diol product using catalyst **1** (Table 1, entry 2).

Table 1. Asymmetric hydrolysis of cyclohexene oxide catalyzed by [(salen)-Co] complexes.^[a]

Entry	Catalyst ^[b] [mol %]	<i>t</i> [h]	Yield ^[c] [%]	<i>ee</i> ^[d] [%]
1	1 (1.5)	3	95	86
2 ^[e]	1 (1.5)	11	98	94
3	3 (1.5)	4	97	93
4	3 (0.5)	12	90	93
5	4 (1.5)	4	91	93
6	4 (0.5)	12	92	93
7	6b (1.5)	36	72	71
8	6b (0.5)	96	16	51

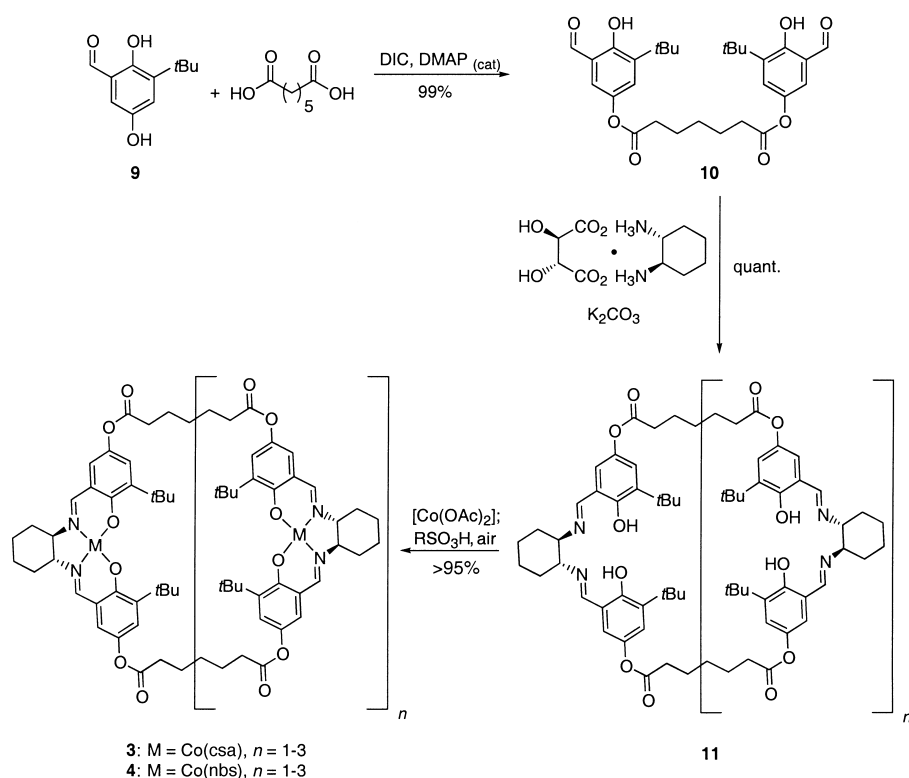
[a] Reactions carried out with [epoxide]₀ = 2.5 M in 1:1 CH₃CN/CH₂Cl₂ at room temperature unless indicated otherwise. See Supporting Information for details. [b] mol % Co relative to epoxide. [c] Yield of isolated product. [d] Determined by chiral GC analysis. [e] Reaction carried out at 4 °C.

Catalysts **3** and **4** were prepared on large scale under chromatography-free conditions from inexpensive components (Scheme 2).^[8] Coupling of phenol **9**^[2] with pimelic acid in the presence of 1,3-diisopropylcarbodiimide (DIC) and a catalytic amount of dimethylaminopyridine (DMAP) provided **10** in 99% purity following extraction and filtration. The free base of (*R,R*)-1,2-diaminocyclohexane was generated in situ from the commercially available tartrate salt and condensed with dialdehyde **10** in quantitative yield. Metal insertion followed by air oxidation in the presence of one equivalent of a sulfonic acid derivative provided the oligomeric catalysts **3** and **4**.^[9] Mass spectral and NMR data indicated the exclusive formation of cyclic oligomers containing 2–4 metal–salen units.

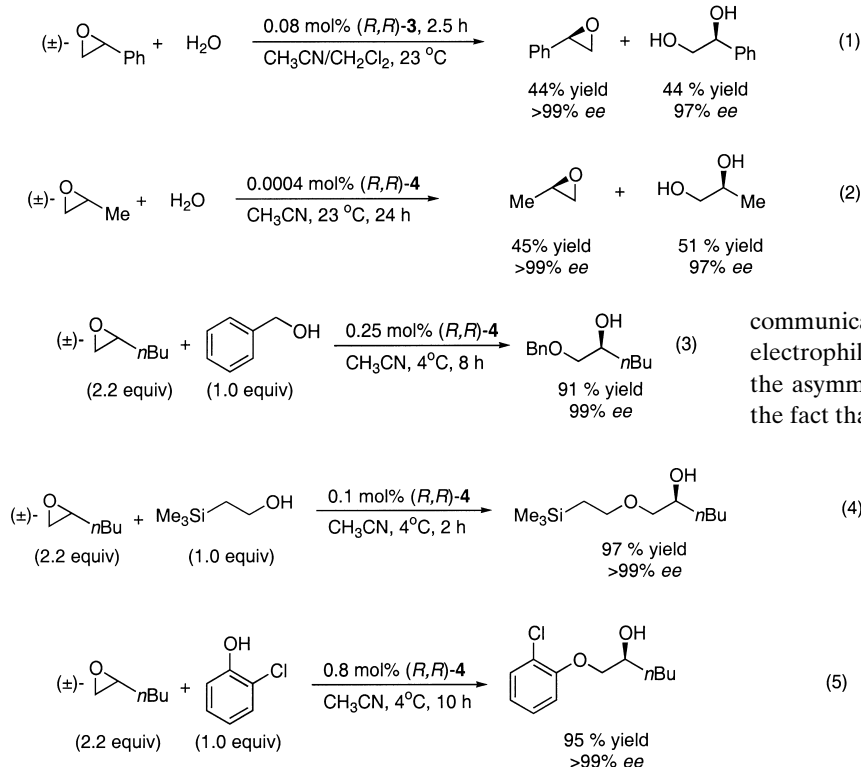
Complexes **3** and **4** were found to display remarkable activity in the hydrolytic kinetic resolution (HKR) of terminal epoxides. Styrene oxide and styrenediol were obtained in high yield and enantiomeric excess after 2.5 h using 0.08 mol % Co [Eq. (1)]. In contrast, under otherwise identical conditions, 24 h were required to obtain epoxide in 99% *ee* using **1**. The results with propylene oxide highlight the practical aspects of reactions using **4**: 1.5 mol epoxide were resolved in 24 h at 23 °C using only 5 mg catalyst to provide 39 g recovered epoxide in >99% *ee* and 59 g diol in 97% *ee* [Eq. (2)].

While complexes **3** and **4** displayed similar activity in the HKR, complex **4** proved superior for the kinetic resolution of terminal epoxides with alcohols and phenols. As demonstrated by the data in Equations (3)–(5), monoprotected 1,2-diols and 1-aryloxy alcohols were synthesized regioselectively in high yield and optical purity. It is noteworthy that the results in Equation (3) were obtained with an eightfold decrease in catalyst loading and a fourfold decrease in reaction time relative to the results obtained previously with **1**.^[2]

Catalyst **1** exists as a complicated mixture of diastereoisomers and ring sizes,^[2] whereas **3** and **4** were synthesized as mixtures of only three compounds (dimer, trimer, and tetramer). It was anticipated that this simplification would aid our efforts to understand the differences in enantioselectivity between oligomeric and monomeric [(salen)Co] com-



Scheme 2. Chromatography-free synthesis of **3** and **4**.



plexes. The discrete components of the catalyst mixture were prepared independently following the strategy shown in Scheme 3.^[9, 10] Catalysts **3a–c** were evaluated in the asymmetric hydrolysis of cyclohexene oxide to determine the effect of ring size on reactivity and selectivity. As revealed by the data in Figure 1, the trimer **3b** is more enantioselective and

reactive than either **3a** or **3c**. As expected, the activity and selectivity of the mixture reflects an average of the mixture's components. Whereas **3b** is clearly the superior catalyst, it is nonetheless remarkable that all three components of **3** provide substantially higher enantiomeric excesses than the monomeric analogue **6b** (Table 1, entries 7 and 8).

In reactions catalyzed by monomeric metal–salen complexes, decreases in product *ee* were observed when catalyst loading was decreased (Table 1, entries 7 and 8). These observations are consistent with a competition between a second-order, bimetallic pathway and a less selective monometallic pathway.^[11] In contrast, the enantioselectivity displayed by **3** and **4** was independent of catalyst loading (Table 1, entries 3 and 4, entries 5 and 6) indicating that a highly selective intramolecular, cooperative process dominates over a range of oligomer concentrations.^[12] Even under optimal conditions, however, monomeric catalysts display lower enantioselectivity than **3** or **4**.

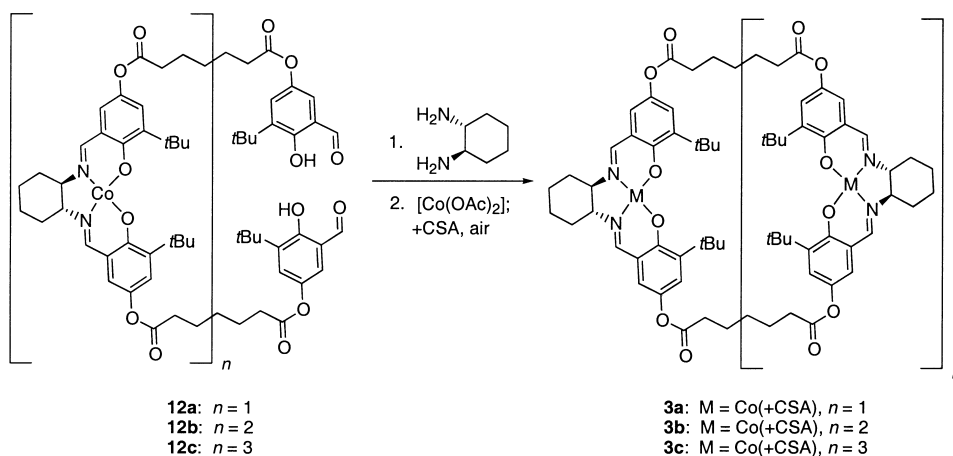
The intervention of a monometallic pathway therefore does not account solely for the observed enhancement in selectivity.

A second factor that may be responsible for the improved enantioselectivity displayed by **3** and **4** involves the range of reactive conformations available to oligomeric versus monomeric complexes. Incorporation of salen units into a cyclic framework may enforce conformations in which the salen units are in the appropriate relative orientation for optimal stereochemical

communication. The chirality of both the nucleophile and electrophile components plays an important role in defining the asymmetric environment in the reaction, as indicated by the fact that nonlinear effects have been observed in both the

HKR^[13] and the [(salen)Cr]-catalyzed addition of HN_3 to *meso*-epoxides.^[14] We propose that the structures of **3** and **4** enforce a selective head-to-tail arrangement of the reacting salen units (Figure 2).^[15] The subtle differences in selectivity observed between **3a–3c** likely reflect differences in available reactive conformations. The data suggest that the trimer combines sufficient rigidity to minimize non-selective pathways while maintaining enough flexibility to access the optimal transition state.

Catalysts **3** and **4** appear to hold significant promise from both a fundamental and a practical perspective. The sterically diverse range of reacting partners accommodated by these catalysts within the confines of a rigidified cyclic architecture is, to the best of our knowledge, unprecedented in asymmetric catalysis. As a result of the ease of their synthesis, we hope



Scheme 3. Synthesis of cyclic oligomeric [(salen)Co] complexes **3a–c**.

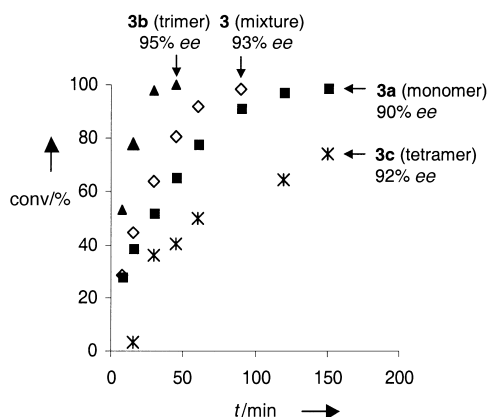


Figure 1. Asymmetric hydrolysis of cyclohexene oxide catalyzed by oligomeric [(salen)Co] complexes. Reactions were carried out with $[\text{epoxide}]_0 = 2.5 \text{ M}$ and 2.5 mol% Co catalyst ($[\text{Co}]_{\text{total}} = 0.0625 \text{ M}$) in 1:1 $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ at 23°C . Conversion determined by GC analysis relative to an internal standard.

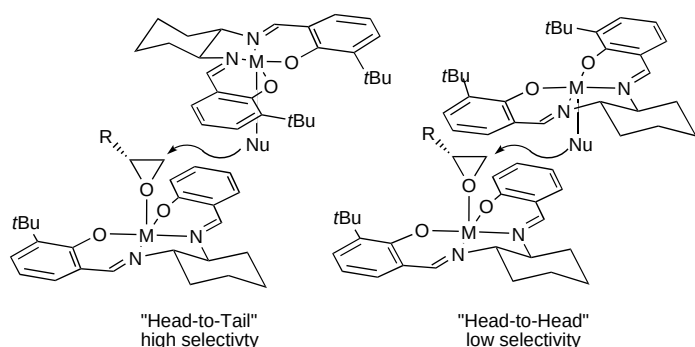


Figure 2. Limiting geometries for the transition state in epoxide ring-opening reaction catalyzed by [(salen)Co] complexes. Some substituents on the aromatic rings are omitted for clarity.

that these oligomeric catalysts will be of immediate utility to the organic chemistry community.

Received: August 30, 2001

Revised: January 31, 2002 [Z17821]

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[3] Calculated by using the formula $\Sigma 3^i$ ($i = 2–6$), where i corresponds to the different oligomers present. There are three stereoisomers of each linker unit (*d*, *l*, and *meso*).

[4] We have also evaluated both shorter (e.g. adipate) and longer (e.g. subarate) linkers. In general, pimelate-based oligosalen systems have proven more reactive and stereoselective.

[5] Recent studies on the hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by monomeric [(salen)Co(O_2CR)] complexes

have demonstrated a critical role for the carboxylate counterion with respect both to catalyst reactivity and stability (J. Hong, D. G. Blackmond, E. N. Jacobsen, work in progress). These results suggest that the carboxylate is in fact retained within the coordination sphere of at least some portion of the catalytically active complex.

[6] Interestingly, the CSA analogue of **1** displayed similar reactivity but diminished selectivity compared to **3**.

[7] A slight cooperative effect is observed between the stereochemistry of the salen unit and that of the camphorsulfonate derivative, with the 1*S*-10-camphorsulfonate proving slightly more effective than its enantiomer in association with the catalyst derived from (*R,R*)-diaminocyclohexane. For example, in the hydrolysis of cyclohexene oxide at room temperature, complex **3** bearing mismatched CSA afforded diol in 92% *ee* (versus 93% *ee* with matched CSA) and 2% lower conversion after 24 h.

[8] Complex **3** has been prepared in our laboratories on a 16 g scale.

[9] See Supporting Information for experimental details and characterization of new compounds.

[10] Attempted synthesis of the macrocycle prior to metal insertion provided a mixture of ring sizes, suggesting that under the conditions of Scheme 2 the formation of **11** is reversible.

[11] The relative rates of a monometallic pathway (v_{mono}) versus a bimetallic pathway (v_{bi}) catalyzed by monomeric complexes are inversely proportional to catalyst concentrations ($[\text{cat}]$) according to $v_{\text{mono}}/v_{\text{bi}} = (k_{\text{mono}}[\text{cat}])/(k_{\text{bi}}[\text{cat}]^2) = (k_{\text{mono}})/(k_{\text{bi}}[\text{cat}])$.

[12] The relative rates of a monometallic pathway (v_{mono}) versus a bimetallic pathway (v_{bi}) catalyzed by **3** and **4** would be independent of catalyst concentration ($[\text{cat}]$) according to $v_{\text{mono}}/v_{\text{bi}} = (k_{\text{mono}}[\text{cat}])/(k_{\text{bi}}[\text{cat}]) = (k_{\text{mono}})/(k_{\text{bi}})$. For preliminary kinetic analysis of reactions of **1**, see ref. [2].

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Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems**

Victor V. Borovkov,* Takunori Harada, Yoshihisa Inoue, and Reiko Kuroda*

To date, the field of supramolecular chirality has attracted much attention in the scientific community, in the context of its direct connection with various natural systems and many practical applications in the areas of catalysis,^[1] nonlinear optics,^[2] polymer and materials science,^[3] molecular recognition,^[4] molecular devices,^[5] and absolute configuration determination.^[6] As noncovalent interactions are the key elements of supramolecular chemistry, there are various

external and internal factors controlling chirality induction in these systems. Among these influences, the phase transition, or aggregation state, takes on particular significance in the light of the wide prospective applications of optically active systems in the solid state.^[7] However, this important factor has not yet been well investigated and rationalized. Here, by applying supramolecular chemistry, solid-state optical spectroscopy, and exciton chirality principles, we describe a novel and intriguing phenomenon of phase-transition controlled chirality induction in a supramolecular system, which consists of an achiral host and a chiral guest.^[8]

Ethane-bridged bis(zinc octaethylporphyrin),^[9] which is in a *syn* conformation in nonpolar solvents (see *syn ZnD* in Figure 1), was chosen as an achiral host molecule. This

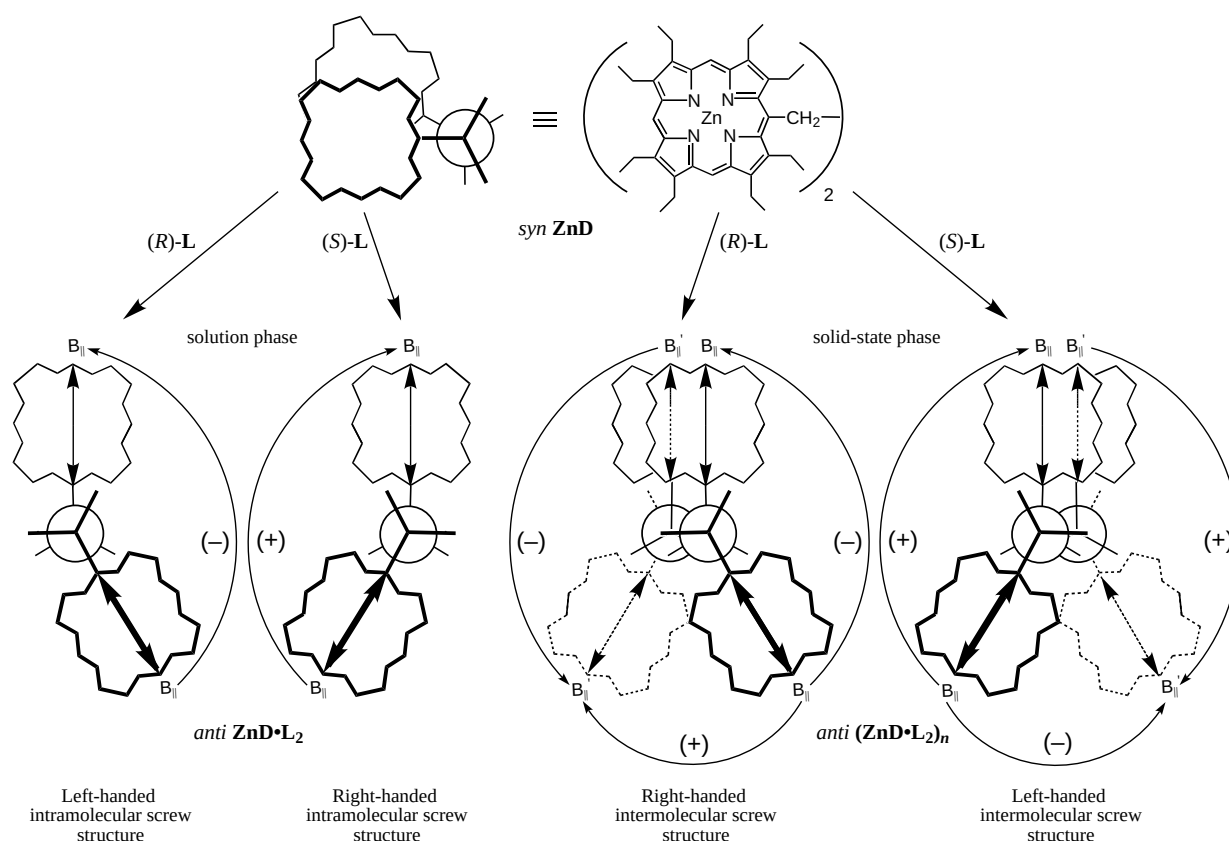


Figure 1. Phase-transition effect on the mechanism of supramolecular chirality induction in achiral *syn ZnD* upon interaction with chiral ligands (**L**) in solution and the solid state. The structures of *anti (ZnD·L₂)_n* are drawn schematically to show the opposing orientation of the intramolecular and intermolecular couplings (other stacked orientations are possible because of rotations of the *anti (ZnD·L₂)_n* monomers against each other).

[*] Dr. V. V. Borovkov, Prof. Dr. R. Kuroda, T. Harada
Kuroda Chiromorphology Project, ERATO, JST
Park Building, 4-7-6 Komaba
Meguro-ku, Tokyo 153-0041 (Japan)
Fax: (+81)3-5452-0599
E-mail: victrb@chiomor.jst.go.jp
ckuroda@mail.ecc.u-tokyo.ac.jp

Prof. Dr. Y. Inoue
Department of Molecular Chemistry, Osaka University
Yamada-oka, Suita, Osaka 565-0871 (Japan)

[**] We thank Dr. G. A. Hembury for critical assessment and assistance in the preparation of this manuscript.

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

compound is well suited for the study of supramolecular chirality induction by chiral ligands (**L**), because of the distinct spectral differences between the initial nonligated *syn ZnD* and the ligand-bonded form (*anti ZnD·L₂*).^[10] This is because of the unique ability of *syn ZnD* to switch conformation from a *syn* (face-to-face) form to an extended *anti* form upon complexation with external ligands in nonpolar solvents. In the case of chiral guests, besides the conformational changes, there is another type of structural deformation in the achiral host, which results in the generation of a screw structure by a steric-repulsion mechanism, and hence the transformation of the point chirality of the guest molecules into the supramolecular helical chirality of

the whole system (see the “solution phase” mechanism in Figure 1). The detailed mechanism, driving forces, equilibria, and various controlling factors of this phenomenon have been thoroughly investigated in the solution phase.^[11] The most interesting and important feature of this host molecule is that the direction of the screw is dictated solely by the stereochemistry of the guest. Thus, when the bulkiness order of the ligand substituents around the chiral center coincides with the substituent-priority rule which determines the absolute configuration, (*R*)- and (*S*)-guests produce corresponding left- and right-handed twists in *anti* **ZnD**·**L**₂, affording negative and positive chirality, respectively (see the “solution phase” mechanism in Figure 1). This makes it possible to use optically inactive *syn* **ZnD** as an effective chirality sensor, which can determine the absolute configuration of optically active compounds (particularly amines and alcohols) in nonpolar solvents by using circular dichroism (CD) spectroscopy.

In the present study, to expand the scope of this versatile chirality sensor and to find new prospective applications, the supramolecular chirogenesis behavior of *syn* **ZnD** upon interaction with the chiral amines **1–4** (listed in Table 1)^[12] has been further investigated in the solid state. The solid-state samples were prepared according to the standard procedure for obtaining a glassy KBr matrix.^[13] Thus, *syn* **ZnD** was first ground with amine **1** (or mixed with amines **2–4**), and then the mixture was thoroughly ground with KBr crystals to a fine powder, which was pressurized to give a transparent KBr disk suitable for optical measurements. Then UV/Vis and CD spectra were recorded in the solid state and compared with those measured in the solution phase.

In the UV/Vis spectra, the maximum ($\lambda_{\text{max}}^{\text{UV}}$) of the B (Soret) band of the initial *syn* **ZnD** in a KBr matrix without amines is essentially the same as that in the solution phase (Table 1), while their spectral profiles are appreciably different. Thus, in the solid state, the B band is broadened, with a shoulder at 414 nm, and has a full-width-at-half-maximum (fwhm) value which is 2.3 times larger than that in the solution phase. This indicates the formation of an associated species of *syn* **ZnD** in the solid state, without *syn*–*anti* conformational switching. In the presence of chiral amines, there are similar spectral changes to those observed in the solution phase. Typical UV/Vis spectra of the amine-containing systems are shown in Figure 2. These transformations include a bathochromic shift

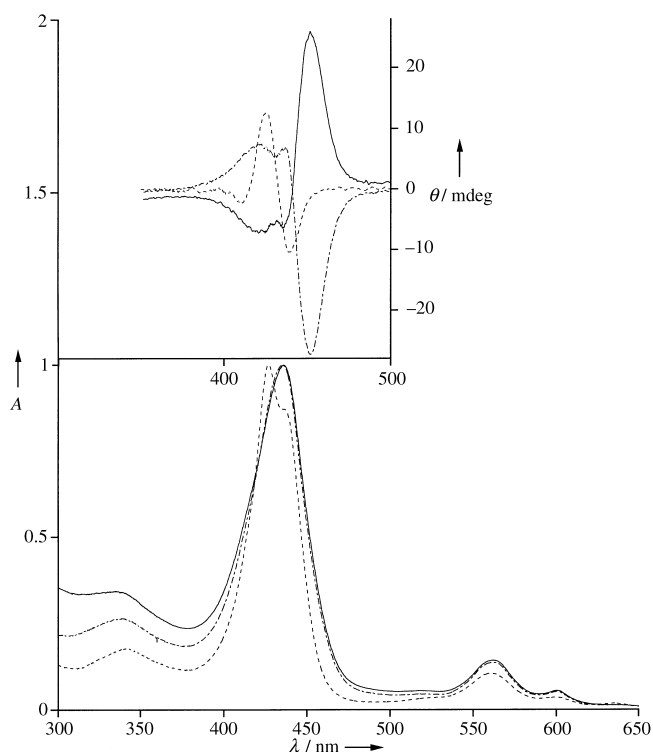


Figure 2. UV/Vis (bottom) and CD (top) spectra of **ZnD** in the presence of **2_R** in CH₂Cl₂ (---), **2_R** in KBr matrix (—), and **2_S** in KBr matrix (•—•). The spectra are normalized to the same optical density.

of the B band by 31–38 nm (Table 1) and the relative enhancement of the Q_{X01} transition intensity, which indicates the same *syn*–*anti* conformational switching to yield the corresponding *anti* species as found in the solution phase.^[11] However, in sharp contrast to the solution phase, the solid-state spectral pattern exhibits an unsplit B band which is broader by a factor of 1.2–1.3, on comparison of the corresponding fwhm values. Of note is that the maximum of this Soret band is very similar to that of the lowest B transition of the split Soret band seen in nonpolar solvents^[14] (except amines **3**). These observations suggest an intermolecular association of the *anti* **ZnD**·**L**₂ molecules to form a stacked *anti* (**ZnD**·**L**₂)_n species.

Simultaneous monitoring of the solid-state complexation by CD spectroscopy also reveals induction of optical activity in

Table 1. UV/Vis and CD spectral data of **ZnD** upon interaction with different chiral amines.

Amine (L)	Solution phase (CH ₂ Cl ₂) ^[a]				Solid-state phase (KBr) ^[b]		
	B bands, $\lambda_{\text{max}}^{\text{UV}}$ [nm] ^[c]	First Cotton effect, $\lambda_{\text{max/min}}^{\text{CD}}$ [nm] ^[c]	Dissymmetry factor at B bands, $\lambda_{\text{max/min}}^{\text{CD}}$ [$g \times 10^3$] ^[d]	$\lambda_{\text{max}}^{\text{UV}}$ [nm]	First Cotton effect, $\lambda_{\text{max/min}}^{\text{CD}}$ [nm]	Dissymmetry factor at B bands, $\lambda_{\text{max/min}}^{\text{CD}}$ [$g \times 10^3$] ^[d]	
none	397	—	—	399, 414(sh)	—	—	
(<i>R</i>)-(+)-bornylamine ^[c] (1_S) ^[f]	427, 437	439	+0.213	437	450	–1.118	
(1 <i>R</i> ,2 <i>R</i> ,3 <i>R</i> ,5 <i>S</i>)-(–)-isopinocampheylamine (2_R) ^[f]	426, 436	439	–0.269	436	452	+1.600	
(1 <i>S</i> ,2 <i>S</i> ,3 <i>S</i> ,5 <i>R</i>)-(+)-isopinocampheylamine (2_S) ^[f]	426, 436	439	+0.269	436	451	–1.640	
(<i>R</i>)-(+)-1-phenylethylamine (3_R)	426, 436	439	–0.216	430	446	+1.361	
(<i>S</i>)-(–)-1-phenylethylamine (3_S)	426, 436	439	+0.180	431	445	–1.630	
(<i>R</i>)-(–)-1-cyclohexylethylamine (4_R)	427, 438	439	–0.134	436	451	+0.208	
(<i>S</i>)-(+)-1-cyclohexylethylamine (4_S)	427, 438	439	+0.130	435	452	–0.209	

[a] $C_{\text{ZnD}} = 2.9\text{--}3.8 \times 10^{-6}\text{ M}$, $C_{\text{L}} = 3.5 \times 10^{-2}\text{--}4.7 \times 10^{-1}\text{ M}$ in CH₂Cl₂. [b] The **ZnD**:**L** molar ratio is within the range of 1:1400–1:1700. [c] The solution phase $\lambda_{\text{max}}^{\text{UV}}$ and $\lambda_{\text{max/min}}^{\text{CD}}$ values are from reference [11a]. [d] $g = \Delta\epsilon/\epsilon$ (or $g = \Delta\text{OD}/\text{OD}$ in the case of solid state samples) where $\Delta\epsilon$ (or ΔOD) is the molar circular-dichroic absorption (or circular-dichroic absorption) of the first Cotton effect obtained from the CD spectrum and ϵ (or OD) is the molar extinction coefficient (or absorption optical density) at the wavelength corresponding to the first Cotton effect obtained from the UV/Vis spectrum. [e] endo-(1*R*)-2-Amino-1,7,7-trimethylbicyclo[2.2.1]heptane. The subscript (*R* or *S*) refers to the absolute configuration of the stereocenter closest to the amine binding group.

the region of the porphyrin B transition,^[15] as in the case of the supramolecular chirogenesis in solution.^[11] However, the solid-state spectral patterns are remarkably different to those of the solution state. Surprisingly, the first Cotton effects showed the opposite sign with much enhanced intensities and bathochromic shifts of up to 6–13 nm, compared with the corresponding phase data obtained for identical amines in the solution phase experiments (see Figure 2, top and Table 1). Furthermore, the CD-spectral profile has a complex shape, rather than the simpler bisignate couplet induced in nonpolar solvents; this probably arises from several overlapping excitonic-type couplets, yielding the enhanced first Cotton effect. The intensities of other Cotton effects are markedly diminished, apparently because of mutual cancellation of couplets of opposite sign, located in the high-energy spectral region. As expected, complexation with the guest of opposite chirality gives the mirror-image induced CD spectrum (Figure 2, top).

Although the detailed mechanism of the supramolecular chirality induction in the solid state is not yet well understood, the chirality-inversion phenomenon can be rationalized on the basis of a simple dimerization model of *anti* **ZnD**·**L**₂ (Figure 1). As reported previously,^[11] in the solution phase the two lowest energy B_{||} transitions in *anti* **ZnD**·**L**₂, the orientation of which determines the sign of the chirality, are coupled intramolecularly in a clockwise fashion upon complexation with *S* amines which, according to the CD exciton chirality method,^[16] corresponds to positive chirality. In the case of *R* amines, the dipole's coupling direction is exactly opposite, which results in negative chirality (see the "solution phase" mechanism in Figure 1). In the solid state, as mentioned above, there is an intermolecular association process, which results in formation of the stacked structures, *anti* (**ZnD**·**L**₂)_n. The simplest stacked species is a dimer of *anti* (**ZnD**·**L**₂)_n where *n* = 2; the schematic structure of which is shown in Figure 1 ("solid-state phase"). Although several structural variations of *anti* (**ZnD**·**L**₂)_n are possible, this type of aggregation mode is considered to be one of the most credible for the following reasons. It was reported^[11a] that supramolecular chirality in the bisporphyrin is induced by the asymmetrical approach of the second ligand to give an atropisomer of *anti* **ZnD**·**L**₂, in which the chiral ligands are positioned on the same side of the porphyrin planes. Therefore, stacking of the two *anti* **ZnD**·**L**₂ molecules to produce a supramolecular, optically active dimeric species can only occur from the opposite, ligand-free sides. Furthermore, an examination of Corey–Pauling–Koltun molecular models, constructed on the basis of the X-ray data obtained for the relevant *trans* isomer of ethylene-bridged bisporphyrin,^[17] reveals that this aggregation mode minimizes intermolecular steric repulsions between the ethyl substituents of the two *anti* **ZnD**·**L**₂ molecules.^[18] It is obvious that, in *anti* (**ZnD**·**L**₂)_n, the orientation of the intramolecularly coupling B_{||} transitions is the same as that of monomeric *anti* **ZnD**·**L**₂ in solution. However, the intermolecular coupling between the B_{||} transition of one molecule and the B'_{||} transition of another molecule in the stacked structure forms an opposing turn: clockwise for *R* amines and anticlockwise for *S* amines (see the "solid-state phase" mechanism in Figure 1), which pro-

duces corresponding positive and negative chirality, according to the CD exciton chirality method.^[16] As the directions of the intramolecular and intermolecular couplings are opposing in *anti* (**ZnD**·**L**₂)_n, it is reasonable to expect a considerable reduction of the induced CD signal^[19] in the high-energy spectral region of the intramolecular couplet, which is observed (Figure 2, top). Simultaneously, the lowest energy Cotton effect at 445–452 nm is intense and apparently arises from the intermolecular coupling, because, as mentioned above, the intramolecular coupling in *anti* **ZnD**·**L**₂ induces a hypsochromically shifted couplet with the position of the first Cotton effect at 439 nm. It is also likely that the intermolecular dipole–dipole interactions in *anti* (**ZnD**·**L**₂)_n induce a more intense CD couplet than intramolecular interactions. Although reliable theoretical treatment of optical activity in bisporphyrins is not yet available, this assumption is supported by a simple dibenzoate model, which shows that the amplitude of the Cotton effects has a parabola-like dependence on the dihedral angle between the coupling transitions, with zero values at 0° and 180°, and a maximum value at around 70°.^[16] Assuming that the coupling dipoles follow this tendency, the angle between intermolecular B_{||} and B'_{||} transitions falls on the steeper, ascending branch of this curve, whilst the angle between intramolecular B_{||} transitions is located on the shallower, descending branch of the curve, which results in enhancement of the intermolecular CD amplitude.

To investigate the influence of the amine structure on supramolecular chirogenesis in the solid state, and to make a reliable comparison of these results with the solution-phase data, the anisotropy (*g*) factors which reflect the pure optical activity of the systems studied are calculated at the wavelength corresponding to the first Cotton effect (Table 1). In general, the *g* values of the solid-state systems are of opposite sign and considerably enhanced (by a factor of 1.6–9.1) in comparison to those of the solution phase; this is caused by the aggregation effect, as discussed above. More interestingly, the solid-state *g* factors are inversely proportional to the solution-phase *g* factors, with a regression line crossing the origin (see Supporting Information). This indicates that, although the apparent cause of the supramolecular chirogenesis is different in solution (intramolecular coupling) and in the solid phase (intermolecular coupling), exactly the same driving forces and controlling parameters (such as ligand structure and binding strength) are operative in both phases. Some deviations from linearity are a result of other factors attributable to the association process and corresponding differences in chirality induction mechanisms.

In summary, this work demonstrates that the phase transition can serve as an effective tool for controlling (and even enhancing) supramolecular chirality induction and inversion in achiral host systems by switching the chirality induction mechanism. Furthermore, correlation of the chirality sign with the absolute configuration of enantiopure ligands opens up an attractive possibility for designing the first chirality sensor in the solid state.

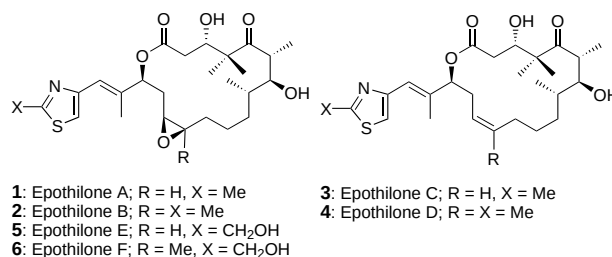
Received: December 3, 2001
Revised: January 28, 2002 [Z18312]

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Stereoselective Total Synthesis of Epothilones by the Metathesis Approach Involving C9–C10 Bond Formation**

Jian Sun and Subhash C. Sinha*

Epothilones A–F (**1–6**, Scheme 1), a new family of natural products initially isolated by Höfle et al. from myxobacteria,^[1] exhibited remarkably high anticancer activity,^[2] especially to taxol-resistant cell lines. These compounds possess a taxol-like mode of action and function through the stabilization of



Scheme 1. Structures of naturally occurring epothilones, **1–6**.

cellular microtubules.^[3] The structural novelty of these compounds and the growing awareness of potential advantages shown by them over taxol, including a higher level of cytotoxicity against multidrug-resistant (MDR) cell lines and better water solubility, spurred interest in their total synthesis.^[4] In the past six years, a large number of publications have emerged on the partial and total synthesis of epothilones.^[5]

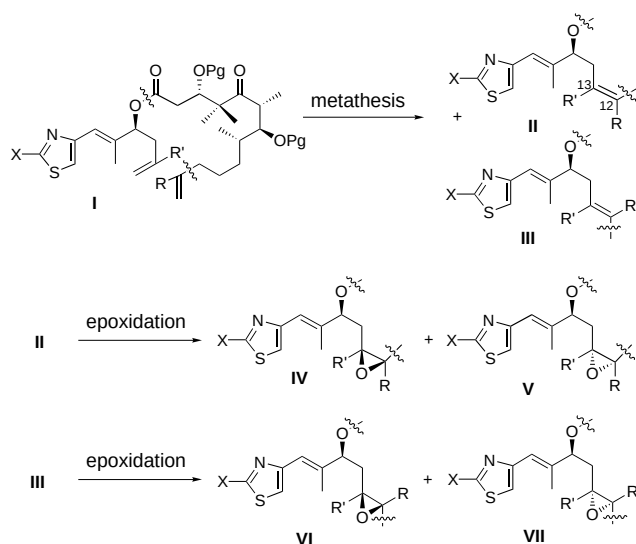
Ring-closing metathesis (RCM) is undoubtedly one of the three most successful and efficient methods used to construct the 16-membered macrolide ring of epothilones.^[6] Compound **I** and its analogues are metathesized to establish the C12–C13 bond of the corresponding macrolide. The metathesis, however, always yields a ≈ 1:1 mixture of the *E* and *Z* isomers (**II** and **III**, Scheme 2).^[7, 8] Furthermore, the subsequent epoxidation of the C12–C13 double bond in **II** and **III** gives a mixture of α and β -diastereoisomers of **IV–VII**, in an approximate ratio ranging from 1:1:1:1 to 3:3:5:1, depending upon the substitution pattern at C12 and C13. Thus, a substantial portion (55–75%) of the precursor is transformed to the undesired products (**V–VII**), which limits the usefulness of this approach to the stereospecific synthesis of epothilones.

To circumvent these problems, we decided to explore RCM of dienes such as **7**, to form the C9–C10 bond after all the

[*] Prof. S. C. Sinha, Dr. J. Sun
 Department of Molecular Biology and the Skaggs Institute for Chemical Biology
 The Scripps Research Institute
 10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
 Fax: (+1) 858-784-8732
 E-mail: subhash@scripps.edu

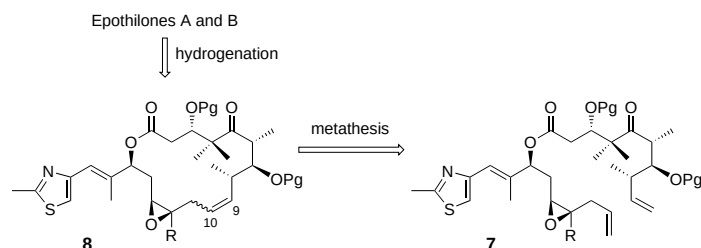
[**] We are thankful to Professor Richard A. Lerner and Samuel J. Danishefsky for helpful discussions. This research was funded by the Scripps Research Institute and the Skaggs Institute for Chemical Biology.

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



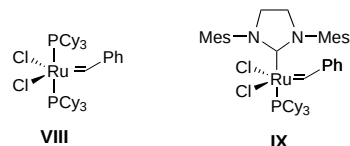
Scheme 2. RCM route to the synthesis of epothilones and their analogues by the formation the of C12–C13 double bond (Pg = H, TBS; X = Me, CH₂OH, SMe; R = H, Me; R' = H, Me, Et; etc).

chiral centers were stereoselectively installed (Scheme 3). A selective hydrogenation of the C9–C10 bond in the expected product **8**, followed by deprotection, should afford epothilones without the formation of undesired isomers.



Scheme 3. Proposed RCM route to the stereoselective synthesis of epothilones A and B by the formation of the C9–C10 bond (epothilone A, Pg = TBS, R = H; and epothilone B, Pg = TBS, R = Me).

The proposed metathesis approach to form the C9–C10 bond in the total syntheses of epothilones was investigated by Danishefsky and co-workers.^[9] In a model system with less functionality around the olefins, the metathesis took place in the presence of various metathesis catalysts, including the Grubbs catalyst **VIII**.^[10] Unfortunately, the metathesis of the fully functionalized

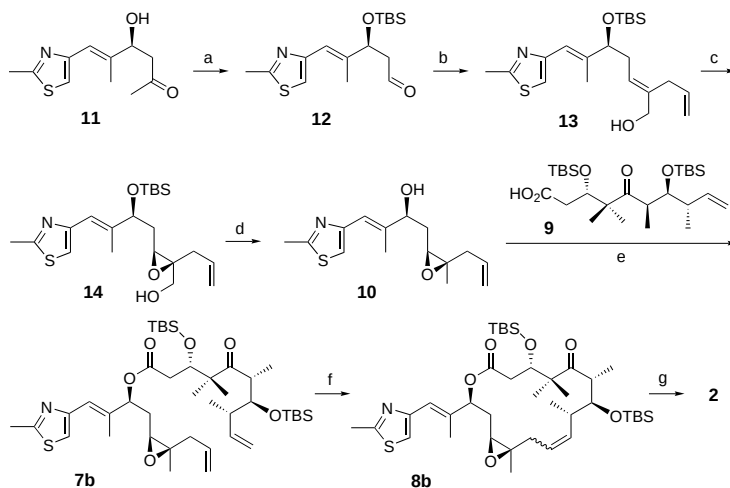


dienes (**7** and analogues) did not take place using **VIII** and other metathesis catalysts known at that time.^[9] Failure of the RCM of compounds **7** and their derivatives was attributed to the highly functionalized C3–C8 region

of the molecule, which renders the macrocyclization energetically unfavorable.

Recently, Grubbs and co-workers reported a very efficient catalyst **IX** that possesses significantly improved activity over **VIII**.^[11] The improved activity of **IX** stems from the greater electron-donating property of the dihydroimidazolylidene ligand than the tricyclohexyl phosphane. We noticed that, unlike with **VIII**, the metathesis of diene **I** (R' = H, R = Me; R' = Me or Et, R = H) could be achieved very simply with **IX** to form a tri-substituted C12–C13 double bond in epothilones **D**, **F**^[12], and 13-alkylepothilones.^[13] Hence, a remarkable capability of the catalyst **IX** to establish multisubstituted C=C bonds by RCM in the epothilone system led us to assume that the RCM at the C9–C10 site could be achieved by this new catalyst. We confirmed this speculation in the synthesis of epothilone **B** (**2**).

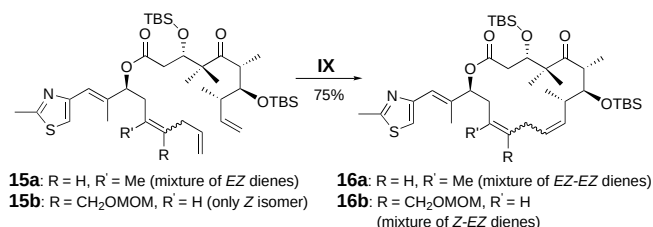
Compound **7b** was synthesized from two immediate precursors, acid **9** and thiazole alcohol **10** (Scheme 4). Compound **9** was synthesized from a known aldol compound in six steps.^[14] The thiazole alcohol **10** was prepared from the aldol compound **11** via the aldehyde **12**^[12] and allylic alcohol **13**.^[15] Sharpless asymmetric epoxidation of **13** afforded the epoxide **14** in more than 95% *ee*. Deoxygenation of the primary alcohol in **14** was achieved as described by Nicolaou et al. in a related system^[15] and then the secondary alcohol was deprotected to afford the alcohol **10**. Esterification of **9** and **10** afforded the key intermediate **7b**. Metathesis of **7b** (3 mM solution in CH₂Cl₂) with 30% of catalyst **IX** in CH₂Cl₂ at reflux temperature took place smoothly. All of the starting compound disappeared completely after 48 h to afford new products, which were characterized as **8b** (*E:Z* = 1:1) from an ¹H NMR spectrum and mass spectrometry analyses. Hydrogenation of the newly formed C9–C10 double bond in **8b**,^[16, 17] followed by deprotection of the *tert*-butylsilyl (TBS)



Scheme 4. Stereoselective synthesis of epothilone **B** (**2**), by the formation of the C9–C10 bond. Key: a) reference [12]; b) reference [15]; c) Ti(*i*OPr)₄, (+)-DET, TBHP, CH₂Cl₂, (85%, >95% *ee*); d) 1. TsCl, Et₃N, CH₂Cl₂, (90%), 2. NaI, acetone, (95%), 3. NaBH₃CN, HMPA, 4. TBAF, THF, (65%); e) EDC, DMAP, CH₂Cl₂, 0°C, 2–8 h, (82%); f) **IX**, CH₂Cl₂, 45°C, 8–48 h, (89%); g) see references [16] and [17]. DET = diethyl tartrate, TBHP = *tert*-butyl hydroperoxide, TsCl = Tosyl chloride, HMPA = hexamethyl phosphoramide, TBAF = tetrabutylammonium fluoride, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

protected hydroxyl groups, resulted in **2** as a single enantiomer.

This metathesis approach could also be utilized for a stereoselective synthesis of other natural and non-natural epothilones. For example, the metathesis of compound **7a** (diastereomeric mixture at epoxide carbons) with 30% of catalyst **IX** in CH_2Cl_2 also took place satisfactorily at reflux temperature, as was the case with **7b**. Consistent with the report by Danishefsky et al., reaction of **7a** with catalyst **VIII** did not afford any desired product.^[9] Compounds **15a** and **15b**, which contained a double bond between C12–C13, were also effectively metathesized by the catalyst **IX** to give the corresponding products (**16a** and **16b**), respectively.^[18] Removal of all of the protecting groups in **16b** with HF.py (py = pyridine), followed by hydrogenation, Sharpless asymmetric epoxidation (SAE), and deoxygenation of the primary hydroxyl group, furnished epothilone B; this is the second successful stereoselective synthesis of epothilone B by metathesis at the C9–C10 bond (Scheme 5).^[19]



Scheme 5. Metathesis of dienes **15a** and **15b**, which results in the formation of the C9–C10 bond; MOM = methoxymethyl.

In summary, we have shown that ring-closing metathesis at the C9–C10 site for the total synthesis of epothilones can be achieved with the Grubbs second-generation catalyst **IX**. In contrast to the Grubbs first-generation catalyst **VIII**, this new catalyst **IX** was found to be highly active, and overcame the high-energy barrier of the intramolecular, macrocyclic ring-closing metathesis of a highly functionalized system such as **7** and **15**. This approach, originally conceived by Danishefsky and co-workers,^[9] now leads to a highly stereoselective synthesis of epothilones by the RCM route as shown by the total synthesis of epothilone B.

Received: August 27, 2001

Revised: November 13, 2001 [Z17798]

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[Co₅(im)₁₀·2MB]_∞: A Metal-Organic Open-Framework with Zeolite-Like Topology**

Yun-Qi Tian, Chen-Xin Cai, Yong Ji, Xiao-Zeng You,*
Shie-Ming Peng, and Gene-Hsiang Lee

Three-dimensional (3D) metal-organic polymers are of intense interest because of their potential novel properties, unique microporous phases, and zeolite-like catalytic features.^[1] To meet the increasing demand for large-pore structures that are suitable for catalyzing reactions of large molecules, successful synthetic strategies have been developed for preparing large, porous metal-organic frameworks.^[2]

As an effective and powerful synthetic strategy, decoration and expansion of the topological networks of some inorganic dense materials have been shown to provide a new generation of highly porous metal-organic polymers.^[3] Our strategy for creating such a metal-organic framework with large pores is based on expanding the zeolite topologies by construction of metal-organic tetrahedral building blocks with four connections. Such building blocks usually lead to a diamondlike topology that is often unstable owing to interpenetration of the framework through enlarged links.^[4] We report here a novel 3D metal-organic framework of a tetrahedral building block, TX₄, in which the T-X-T angle is about 145°. In this structure, the TX₂ compound was prepared with a zeolite-like topology. Imidazole was chosen as a linker X since the two-coordinate N atoms of this bidentate ligand are oriented at an angle of about 144°, which is very close to the Si-O-Si angle of 145° in zeolites. For the four-connected nodes in the framework, we considered the cobalt(II) ion to be the best candidate for the T atom and that [Co(im)₄]²⁻ would be a suitable building block. A different, structure-defined 3D polymer of this building block has been reported previously as a neutral framework.^[5] This framework, however, has no pore opening, and furthermore, it exhibits neither the diamond topology nor the zeolite structure.

The new compound [Co₅(im)₁₀·2MB]_∞ (**1**) was synthesized under solvothermal conditions by using piperazine (PZ) as the structure-directing agent and 3-methyl-1-butanol (MB) as the solvent and space-filling agent. Though not observed in the crystalline structure, the piperazine apparently serves some structure-directing role since parallel reactions with different structure-directing agents result in different networks. Furthermore, a precipitate isolated after 12 h at room temperature prior to solvothermal reaction, exhibits an IR spectrum with a distinctive signature for an NH stretch. The

violet needle crystals of **1** were characterized by IR spectroscopy, elemental analysis, and by single-crystal X-ray structure analysis.

The X-ray structural analysis showed that the neutral 3D framework of [Co₅(im)₁₀·2MB]_∞ (**1**)^[6] is composed of 4-connected tetrahedral building blocks [Co(im)₄]. There are five T atoms in the asymmetric unit (Figure 1) and 20 T atoms in the

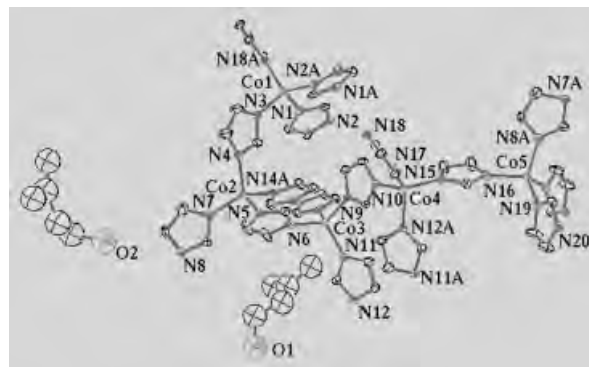


Figure 1. Coordination geometry of cobalt atoms (T atoms) in the asymmetric unit of compound **1**. Thermal ellipsoids are at 50% probability level. Selected bond lengths [Å] and angles [°] and Co...Co distances [Å]: Co1-N1 1.972(3), Co1-N3 1.983(4), Co1-N18A 1.994(4), Co1-N2A 1.990(4); N1-Co1-N3 113.0(3), N1-Co1-N18A 111.6(4), N1-Co1-N2A 105.3(4), N3-Co1-N18A 108.5(5), N2-Co1-N2A 113.3(4), N18A-Co1-N2A 104.9(5); Co1...Co2 6.030(5), Co2...Co3 5.972(5), Co3...Co4 5.898(5), Co4...Co5 5.891(5).

unit cell together with eight structurally defined MB molecules. This framework exhibits a zeolitic topology, analogous to all silicate neutral frameworks, although the specific connectivity represents a topology that to the best of our knowledge has not previously been observed in molecular sieve chemistry (Figure 2). The structure of **1** contains 5- and

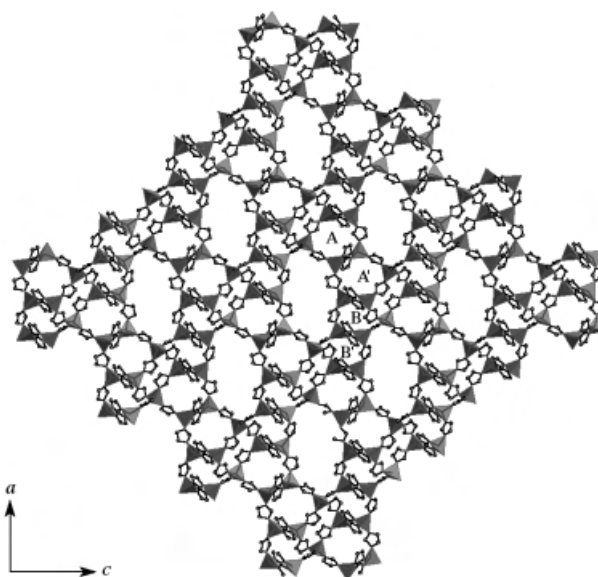


Figure 2. Polyhedral packing diagram of **1** showing the zeolite-like topology; A, A', B, B' are channels of the corresponding chains viewed down [010]. The hydrogen atoms and the guest MB molecules are omitted for clarity.

[*] Prof. X.-Z. You, Y.-Q. Tian, C.-X. Cai, Y. Ji
State Key Laboratory of Coordination Chemistry
Coordination Chemistry Institute, Nanjing University
Nanjing 210093 (PR China)
Fax: (+86)25-3314502
E-mail: xyz@netra.nju.edu.cn
Prof. Dr. S.-M. Peng, G.-H. Lee
Department of Chemistry
National Taiwan University, Taipei (Taiwan)

[**] This work was funded by the State Key Project of Fundamental Research (No. G200077500) and the Natural Science Foundation of China. We thank Prof. Dr. Ren-Gen Xiong for production of figures. im = imidazole; MB = 3-methyl-1-butanol.

6-rings, which are made of two different chain units (chain A and chain B). These chains run along the *b* axis, and are arranged AA'BB' along the *a* axis by using the common edges to form corrugated sheets (A' and A, and B' and B are related by C_2 symmetry). These sheets, which are related to each other by a center of inversion, share common vertices on the peaks of the corrugated sheets. This results in the formation of the 3D framework with sequences of parallel square rings and elliptical 8-rings. The latter forms one-dimensional (1D) channels (Figure 3), which intersect each

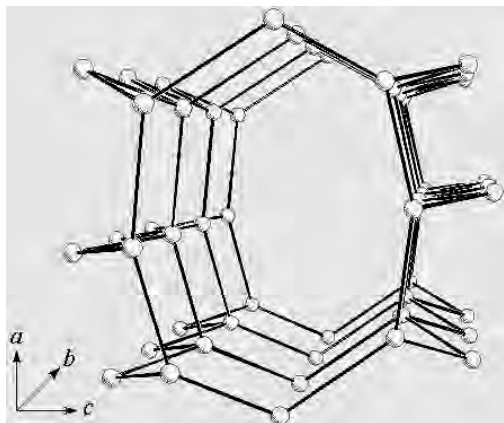


Figure 3. Ball-and-stick representation of the tubular building unit of **1**. Spheres: Co; sticks: imidazolate groups.

other through offset 8-ring openings in the (110) direction and 6-ring openings in the (001) direction. The channel openings are $16.89 \text{ \AA} \times 11.65 \text{ \AA}$. When van der Waals radii of the atoms are taken into account, these openings are $9.42 \text{ \AA} \times 3.87 \text{ \AA}$. If a structure with zeolite or zeolite-like topology with 10- or even larger rings could be created by using the cobalt imidazolate, this would likely lead to materials with mesoporous phases.

The MB-free compound **2** was prepared by refluxing compound **1** in ethanol for 4 h and then evacuating the product at 5×10^{-5} Torr for 6 h at room temperature. The X-ray structure of **2**^[6b] shows that the MB-free compound still maintains the framework symmetry of compound **1**. However, more disordered imidazolates are observed in **2**, and ethanol molecules are found (ca. 50% occupancy) in the chain A channels. These ethanol molecules can be then easily removed by heating the sample at 70°C under vacuum.

Thermal gravimetric analysis (TGA) of **1** under a nitrogen stream^[7] shows release of guest MB molecules between 130 – 220°C leading to a weight loss of 15%, which corresponds to the loss of all guest MB molecules. Above 220°C , the sample shows no further weight loss up to 430°C at which temperature the compound decomposed. The sample of fully evacuated **1** maintains its crystalline transparency, and the powder X-ray diffraction patterns are identical to that of the as-synthesized compound **1**, only with weakened intensities. However, when the above sample is soaked in MB for several hours, the intensities of the diffraction patterns recover. TGA of **2** shows release of ethanol with a weight loss of about 2% up to 130°C , while the framework is stable up to 430°C .

Refluxing **1** in toluene or xylene for 24 h led to a replacement of the MB molecules in **1** with toluene or xylene. The presence of toluene or xylene was detected by the new bands in the IR spectra and confirmed by the high carbon value in the elemental analyses of the corresponding samples. These solids with new guests also maintained their crystal forms and transparency. The above results reveal the robust framework of **1** and show it may endure a rather high-temperature operating condition for catalysis and separation. Therefore we consider that the cobalt imidazolate **1** is likely a real metal-organic zeotype.^[8]

Experimental Section

1: $\text{Co}(\text{Ac})_2 \cdot 4\text{H}_2\text{O}$ (2.5 mmol), imidazole (5 mmol), and piperazine (2.5 mmol) were stirred in 3-methyl-1-butanol (30 mL) at room temperature for 12 h to give a precipitate. This heterogeneous mixture was then placed in a Teflon-lined steel autoclave and heated at 140°C for 24 h. The resulting impure dark purple single crystals of **1** are stable in air and insoluble in water and common organic solvents except organic acids such as formic and acetic acid. Further purification gave **1** in about 60% yield. **1:** Elemental analysis (%) for $[\text{Co}_5(\text{im})_{10} \cdot 2\text{MB}]_\infty$: calcd: C 42.08, H 4.77, N 24.54; found: C 41.81, H 4.40, N 24.38; FT-IR (KBr): $\tilde{\nu} = 3129$ (w), 3104 (w), 2956–2870 (m), 1489 (s), 1469 (s), 1084 (vs), 953 (s), 831 (m), 756 (s) 668 (s) cm^{-1} . **2:** Elemental analysis (%) for $[\text{Co}_5(\text{im})_{10} \cdot 0.5\text{EtOH}]_\infty$: calcd: C 37.67, H 3.37, N 28.35; found: C 38.18, H 3.78, N 27.95; FT-IR (KBr): $\tilde{\nu} = 3129$ (w), 3104 (w), 2955 (w), 1489 (s), 1468 (s), 1083 (vs), 952 (s), 829 (m), 754 (s) 667 (s) cm^{-1} .

Received: August 29, 2001

Revised: December 10, 2001 [Z17819]

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- [6] a) A violet crystal of $[\text{Co}_5(\text{im})_{10} \cdot 2\text{MB}]_\infty$ (**1**) was selected for X-ray structural analysis on a Bruker SMART CCD diffractometer at $150(1) \text{ K}$. The compound crystallized in the space group $P2_1/n$, monoclinic, dimensions $0.37 \times 0.10 \times 0.07 \text{ mm}$, $a = 24.3406(8)$, $b = 9.4526(3)$, $c = 24.8470(8) \text{ \AA}$, $\beta = 91.877(1)^\circ$, $V = 5713.8(3) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.327 \text{ Mg m}^{-3}$, $\lambda = 0.71073 \text{ \AA}$, $\mu(\text{Mo K}\alpha) = 1.470 \text{ mm}^{-1}$, $F(000) = 2340$. A total of 43981 reflections were collected in the range of $1.15^\circ \leq \theta \leq 26.40^\circ$, of which 11707 were unique reflections and 6306 with $I \geq 2\sigma(I)$ were collected for the analysis. The structure was solved and refined by full-matrix least-squares on F^2 values (SHELXL-97). Non-hydrogen atoms (excluding those of solvent molecules) were refined anisotropically, of which C10, C11 (C10', C11') are disordered and were modeled in 70% (30%) SOF. Hydrogen atoms were fixed at calculated positions and refined by using a riding mode. The final indices were $R1 = 0.0688$, $Rw2 = 0.230$ with goodness-of-fit = 1.027. b) A violet crystal of $[\text{Co}_5(\text{im})_{10} \cdot 0.5\text{EtOH}]_\infty$ (**2**) was selected for X-ray structure analysis on a Bruker SMART CCD diffractometer at

293(2) K. The compound crystallized in the space group $P2_1/n$, monoclinic, dimensions $0.35 \times 0.10 \times 0.08$ mm, $a = 24.246(5)$, $b = 9.5182(19)$, $c = 24.685(8)$ Å, $\alpha = 90.96(3)^\circ$, $V = 5696(2)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.153$ Mg m⁻³, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 1.463$ mm⁻¹, $F(000) = 1992$. A total of 34441 reflections were collected in the range of $1.65^\circ \leq \theta \leq 28.02^\circ$, of which 13040 were unique reflections and 4517 with $I \geq 2\sigma(I)$ were collected for the analysis. The structure was solved by full-matrix least-squares on F^2 values (SHELX-97). Non-hydrogen atoms (excluding disordered and solvent atoms) were refined anisotropically. The disordered atoms were modeled in 50% SOF. Hydrogen atoms were fixed at calculated positions and refined by using a riding mode. The final indices were $R1 = 0.0561$, $Rw2 = 0.1149$ with goodness-of-fit = 1.023. CCDC-168798 (**1**) and CCDC-168799 (**2**) 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 (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).

[7] Thermal analyses were carried out using a TA-SDT 2960 apparatus at a heating rate of 5 K min⁻¹ from 20 to 1000 °C under a flux of nitrogen: 6.8505 mg of the sample **1** and 11.9348 mg **2** were used for the measurement.

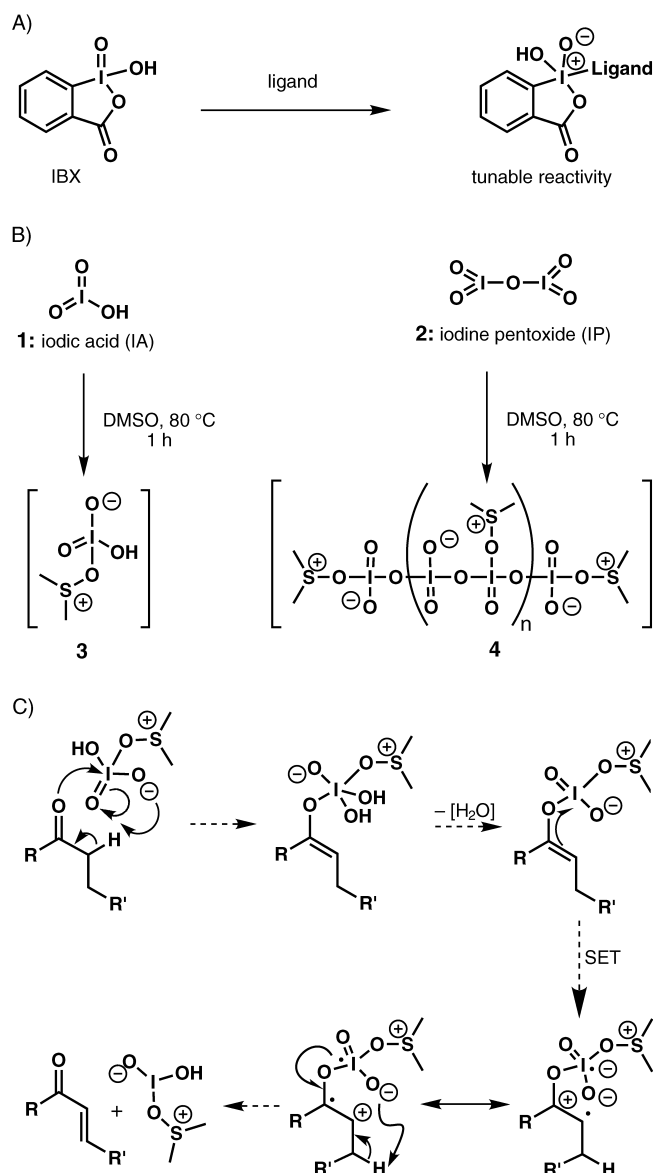
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HIO₃ and I₂O₅: Mild and Selective Alternative Reagents to IBX for the Dehydrogenation of Aldehydes and Ketones**

K. C. Nicolaou,* Tamsyn Montagnon, and Phil S. Baran

Although the chemistry of iodine(III) and iodine(VII) reagents has been extensively explored,^[1] that of the iodine(V) manifold, which includes reagents such as 1-hydroxy-1,2-benziodoxal-3(1H)-one-1-oxide (IBX) and Dess–Martin periodinane (DMP), remained until recently almost entirely relegated to being a source of reliable agents for the simple oxidation of alcohols and for a number of closely related processes.^[2] However, a recent discovery that stems from endeavors in total synthesis in our laboratories^[3] has opened the door to the development of a number of novel iodine(V)-mediated reactions.^[4–11] Furthermore, detailed mechanistic

studies into one of these processes, the IBX-mediated dehydrogenation of ketones and aldehydes,^[10, 11] led to the recognition of the importance of the ligand appended to the iodine nucleus in this and other SET-based process (Scheme 1 A).^[7] Armed with this information, we were able to tune the reactivity at the iodine nucleus by using a variety of *N*-oxide ligands, and hence developed a mild room-temperature variant of the original IBX dehydrogenation with expanded functional group tolerance.^[12] With such dramatic changes in reactivity patterns on changing the ligand from THF^[7, 8] or DMSO^[10, 11] to an *N*-oxide,^[12, 13] we began to question the role of all the substituents on the iodine nucleus, including the aromatic core. Herein we report initial results that probe the latter question and provide us with a number of economic, commercially available, and safe iodine(V) dehydrogenation agents whose structures contain no aromatic moiety.



Scheme 1. A) The tunable reactivity of IBX by using different ligands prompted the investigation of the role of the aromatic moiety. B) This led to development of **3** and **4** as dehydrogenating agents. C) Postulated mechanism of action.

[*] Prof. Dr. K. C. Nicolaou, Dr. T. Montagnon, Dr. P. S. Baran
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

[**] We thank Dr. D. H. Huang, Dr. G. Suizdak, and Dr. Raj Chahda for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, fellowships from GlaxoWellcome (T.M.) and the National Science Foundation (P.S.B.), and grants from Amgen, Array Biopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

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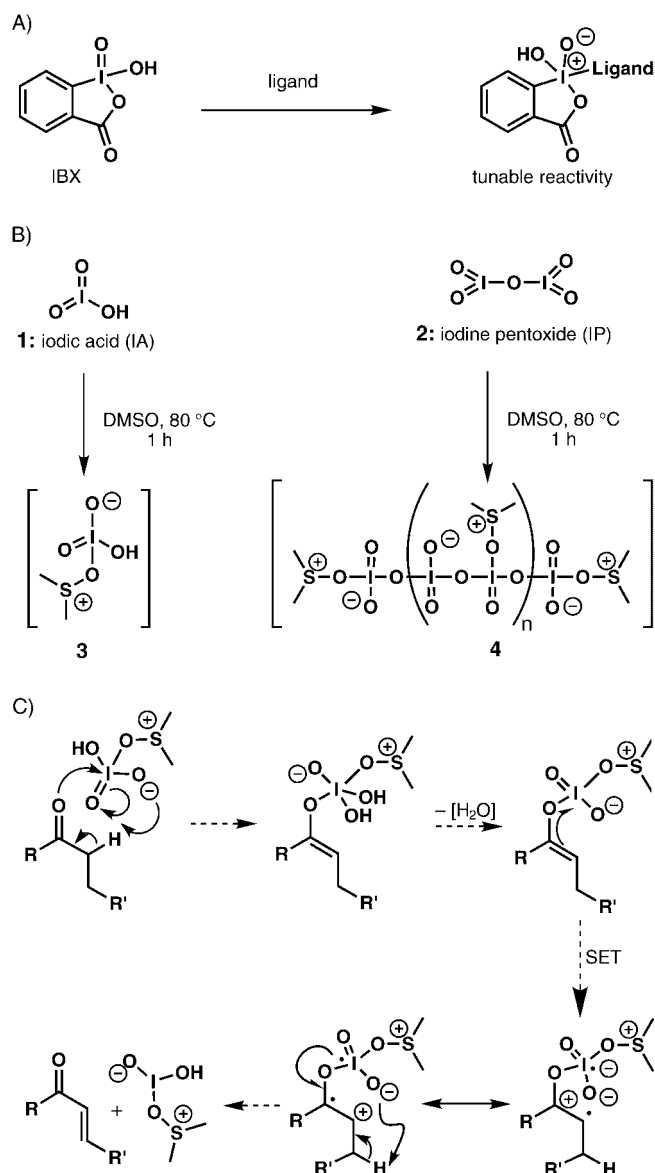
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studies into one of these processes, the IBX-mediated dehydrogenation of ketones and aldehydes,^[10, 11] led to the recognition of the importance of the ligand appended to the iodine nucleus in this and other SET-based process (Scheme 1 A).^[7] Armed with this information, we were able to tune the reactivity at the iodine nucleus by using a variety of *N*-oxide ligands, and hence developed a mild room-temperature variant of the original IBX dehydrogenation with expanded functional group tolerance.^[12] With such dramatic changes in reactivity patterns on changing the ligand from THF^[7, 8] or DMSO^[10, 11] to an *N*-oxide,^[12, 13] we began to question the role of all the substituents on the iodine nucleus, including the aromatic core. Herein we report initial results that probe the latter question and provide us with a number of economic, commercially available, and safe iodine(V) dehydrogenation agents whose structures contain no aromatic moiety.



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[*] Prof. Dr. K. C. Nicolaou, Dr. T. Montagnon, Dr. P. S. Baran
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

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To determine the role of the aryl moiety in the reactivity of IBX, we evaluated the most simple iodine(V)-based reagents: HIO_3 (**1**, iodic acid, IA) and its anhydride I_2O_5 (**2**, iodine pentoxide, IP) (Scheme 1 B). Both were efficient reagents for the mild and chemoselective dehydrogenation of carbonyl compounds. Despite their extensive use in industry^[14] and their commercial availability,^[15] IA and IP have rarely been employed in organic synthesis. Their industrial applications and studies conducted at elevated temperatures^[16] strongly suggest that these agents are particularly stable oxidants. This feature is perhaps related to the stabilization attained through the extensive secondary bonding networks present in the solids and, at least partially, maintained in solution.^[17] There is, therefore, no indication that they pose the same detonation risk that is claimed for IBX.^[18] Our first exploration of this chemistry probed the ability of these simple reagents to oxidize alcohols to carbonyl-containing compounds; we found

that alcohol substrates are inert to these oxidants. In light of the results elaborated below, initial coordination of the substrate is unlikely to be responsible for this lack of reactivity and, therefore, a possible explanation could be that the oxide ligand is less basic than the one on IBX. We reasoned that dehydrogenation might still be feasible (for a mechanistic rationale, see Scheme 1 C), and by analogy to our studies with IBX,^[11] we prepared the DMSO complexes of IA and IP (Scheme 1 B, **3** and **4**, respectively).

Gratifyingly, the IA·DMSO (**3**) and IP·DMSO (**4**) complexes are remarkably mild and efficient oxidants, and can be used for dehydrogenation of both aldehydes and ketones (Table 1). Although equally efficient, we favored the use of IA in these reactions over its more expensive anhydride IP. Moreover, since the oxidation reactions tend to produce varying amounts of detrimental iodine as a by-product, cyclohexene was added as a cosolvent. Under optimal

Table 1. Facile dehydrogenation of ketones and aldehydes using HIO_3 (IA) and I_2O_5 (IP).^[a]

Entry	Substrate	Product	IA [equiv]	Temperature	Time [h]	Yield [%] ^[b]
1			1.8	50 °C	18	88
2			1.1	50 °C	8	95
3			1.2	50 °C	4	88
4			1.7	50 °C	6	78
5			1.7	50 °C	6	82 ^[c]
6			2.5	65 °C	18	82
7			1.7	45 °C	6	74
8			1.4	50 °C	6	90
9			1.5	50 °C	12	92
10			1.2	50 °C	12	77

[a] Reactions were carried out on a 0.1–1.5-mmol scale in DMSO. [b] Yield of isolated chromatographically pure compound. [c] Starting material is commercially available as a mixture of regioisomers; products were separated by chromatography.

conditions, 1.3–2.5 equivalents of **3** (1M solution in DMSO, prepared by heating a solution of IA in DMSO at 80 °C for 1 h) and cyclohexene (0.25 mLmmol of substrate) are used. The reaction mixture, which included a further dilution with DMSO (1.0 mLmmol of substrate), was heated in a sealed tube at 45–65 °C for 5–12 h, with light excluded from the vessel. Standard reagent grade DMSO and cyclohexene were used, and the reaction was impervious to moisture or air. The workup was operationally very simple and provided pure products after flash column chromatography.

The scope of the reaction appears to be similar to the IBX-mediated dehydrogenation.^[10, 11] One difference, however, was the remarkable ease with which the indanone nucleus could be oxidized (Table 1, entries 4 and 5) in high yields. This particular transformation has challenged the more traditional dehydrogenation techniques, which give poor yields and often unwanted by-products.^[19] Mindful of the challenges associated in some instances with the preparation of simple enones on a large scale^[20] in terms of expense and practicality, we tested the present method in this arena. Cyclopentanone was cheaply and efficiently converted into its enone in 74 % yield on a 0.15-mole scale (Table 1, entry 7). We took advantage of the inertness of alcohols towards **3** and selectively dehydrogenated a ketone in the presence of an unprotected alcohol (Table 1, entry 9). To confirm that this result was not related to the steric environment of the alcohol in this example, an intermolecular competition experiment was undertaken in which *tert*-butylcyclohexanone was smoothly converted into *tert*-butylcyclohexenone in the presence of one equivalent of a primary alcohol (Scheme 2). No aldehyde was observed in the reaction (monitored by means of ¹H NMR spectroscopy).

Table 2. Selected data for **5** and **6** (determined by means of NOE and ROESY NMR spectroscopic analysis).

5: Bright yellow oil; *R*_f = 0.24 (silica gel, hexane/diethyl ether 9:1); IR (film): $\tilde{\nu}_{\text{max}}$ = 3082, 2923, 2861, 1714, 1580, 1542, 1484, 1379 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, *J* = 6.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 5.91 (d, *J* = 6.2 Hz, 1H), 2.26 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 195.9, 146.0, 145.0, 136.4, 133.9, 127.0, 116.1, 16.6; high-resolution MS (matrix-assisted laser desorption/ionization (MALDI)): calcd for C₁₀H₇OBrNa [*M*+Na⁺]: 244.9572; found: 245.0455; MS (electrospray ionization (ESI)): [*M*+H⁺]: 223.

6: Bright yellow oil; *R*_f = 0.56 [silica gel, hexane/diethyl ether 9:1]; IR (film): $\tilde{\nu}_{\text{max}}$ = 2921, 2852, 1702, 1659, 1644, 1538, 1453, 1385 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, *J* = 5.9 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.90 (d, *J* = 5.9 Hz, 1H), 2.44 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 198.8, 147.7, 144.5, 136.6, 136.2, 128.6, 127.9, 114.3, 16.6; HRMS (MALDI) calcd for C₁₀H₇OBrNa [*M*+Na⁺]: 244.9572; found: 245.0448; MS (ESI): [*M*+H⁺]: 223.

To improve our understanding of the nature of these iodine(v)·DMSO complexes, we prepared crystalline **4** by lyophilization of a solution of **4** in DMSO (1.2M).^[21] The ORTEP representation (Figure 1), obtained from X-ray crystallographic analysis of this complex, shows that **4** self-assembles into a remarkable helix in the solid state. Within the “grooves” of this helix, additional molecules of DMSO are bound to the iodine nuclei by secondary bonds. Based on the observed bond lengths for this assembly, we believe that the complex in solution can be depicted as shown in Scheme 1.

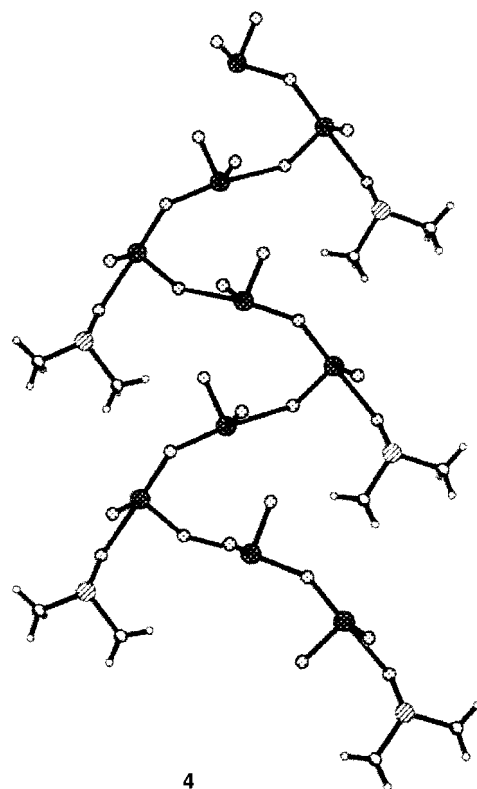
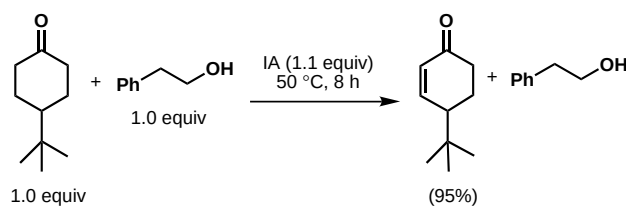


Figure 1. ORTEP representation of the helical IPwDMSO complex (**4**).



Scheme 2. Unprotected alcohols are inert to the reaction conditions utilized in this procedure.

In conclusion, we have demonstrated the unique mild and efficient nature of HIO₃ and its anhydride I₂O₅ as commercially available, more atom-efficient, and safer alternatives to IBX for the dehydrogenation of carbonyl compounds. Furthermore, these IBX surrogates are highly chemoselective, and effect smooth dehydrogenations at 45–65 °C in the presence of a variety of sensitive functionalities, including unprotected alcohols. We have also shown that the procedure developed here is amenable to large-scale operations, with high efficiency and cost effectiveness. Our investigations now center on exploring other possible transformations of these versatile reagents and their complexes with a variety of ligands.

Received: December 21, 2001 [Z18429]

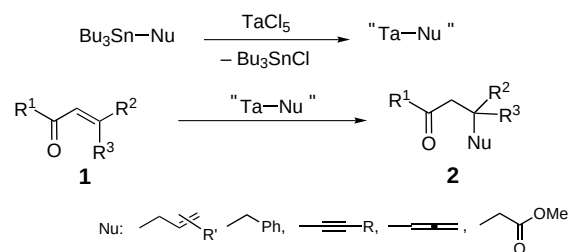
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Generation of Organotantalum Reagents and Conjugate Addition to Enones**

Ikuya Shibata,* Takeyoshi Kano, Nobuaki Kanazawa, Shoji Fukuoka, and Akio Baba*

Organotin compounds are good precursors for generating active organometallic agents through transmetalation.^[1, 2] For example, active allylic titanium complexes generated from allylic tin complexes have performed effective allylation of carbonyl compounds.^[1] In contrast, generation and synthetic use of similar early transition metal complexes such as tantalum reagents^[3] have not been reported so far, although Ta–C bonds are known to be moderately reactive to electrophiles.^[4, 5] We report here on the preparation of active tantalum reagents by the transmetalation of organotin compounds with tantalum(v) chloride. Of particular interest is that certain tantalum reagents promote the conjugate allylation of enones (Scheme 1).



Scheme 1. Generation of an active tantalum–nucleophile complex and subsequent addition to an enone.

Compared with the direct allylation of carbonyl groups, little has been reported on the selective conjugate allylation of enones.^[6] The only choice for this purpose has been the Hosomi–Sakurai reaction (allylsilane and TiCl_4).^[7a] Later, modified reagents such as allylbarium^[7b] and allylcopper^[7c] were developed to avoid strong acidic conditions. However, with these modified reagents the allylation of acyclic enones is far more difficult than that of cyclic ones. The present system could be the method of choice for conjugate addition of allylic nucleophiles including sterically hindered ones to enones.^[8]

The results of the conjugate allylation of enones, both acyclic and cyclic substrates, are given in Table 1. Under the conditions described in the Experimental Section, benzalacetone (**1a**) was allylated to give the conjugate adduct **2a** in 91% yield (entry 1, Table 1). The yield decreased to 50%

[*] Dr. I. Shibata, Prof. Dr. A. Baba, T. Kano, N. Kanazawa, S. Fukuoka
Department of Molecular Chemistry & Frontier Research Center
Graduate School of Engineering, Osaka University
2–1 Yamadaoka, Suita, Osaka, 565-0871 (Japan)
Fax: (+81) 6-6879-7387
E-mail: shibata@ap.chem.eng.osaka-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of the Japanese Government. We thank Mr. H. Moriguchi, Faculty of Engineering, Osaka University, for assistance in obtaining mass spectra.

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Table 1. Conjugate allylation of enones **1** according to Scheme 1 (Nu = allyl, R³ = *E* or *Z* H).^[a]

Entry	Starting compound	R ¹	R ^{2[b]}	Solvent	Product	Yield [%]
1	1a	Me	Ph	CH ₃ CN	2a	91 (50 ^[d])
2	1a	Me	Ph	CH ₂ Cl ₂	2a	trace
3	1a	Me	Ph	THF	2a	49
4	1a	Me	Ph	Et ₂ O	2a	7
5	1b	Ph	Ph	CH ₃ CN	2b	99
6	1c	Ph	Me	CH ₃ CN	2c	63
7	1d	Ph	H	CH ₃ CN	2d	48
8	1e	Ph	PhMeCH	CH ₃ CN	2e	63 ^[d]
9	1f	Et	Me	CH ₃ CN	2f	83
10	1g	-(CH ₂) ₂ -		CH ₃ CN	2g	56
11	1h	-(CH ₂) ₃ -		CH ₃ CN	2h	81

[a] Conditions: allyltributyltin (2 mmol), TaCl₅ (1 mmol), enone **1** (1 mmol), solvent (1 mL). [b] Entries 1–9: *E* isomers; entries 10 and 11: *Z* isomers. [c] Allyltin (1 mmol). [d] d.r. = 89:11.

when one instead of two equivalents of the allyltin reagent was used. Acetonitrile is the solvent of choice (see entries 2–4 for the results with other solvents). Aromatic and aliphatic enones are similarly applicable to this conjugate allylation to give **2b–2h** (entries 5–11). In all cases, the 1,2-adduct was not obtained.

The use of allyltrimethylsilane in place of allyltri-*n*-butyltin under the identical conditions resulted in lower yield of **2b** (27 %), perhaps because TaCl₅ does not interact with allylsilane. The reaction of allylmagnesium bromide, TaCl₅, and **1b** in THF at –40 °C afforded only 1,2-adduct (34 %). Furthermore, attempted allylation with allyltitanium generated from allyltri-*n*-butyltin and TiCl₄ did not afford any products. Thus, the allyltin–tantalum system seems to be the one efficient combination for conjugate allylation.

That the transmetalation of the tin species with TaCl₅ is facile is evident in Table 2. When equimolar amounts of TaCl₅ and allyltri-*n*-butyltin were stirred at –40 °C in THF or CH₃CN for 30 min, quantitative yields of *n*Bu₃SnCl were obtained but the transmetalation is faster in the latter solvent (entries 1 and 2, Table 2). When an excess of allyltin was used, *n*Bu₃SnCl was formed in over 100 % yield based on TaCl₅, which indicates that several Ta–Cl bonds are responsible for the transmetalation (entries 3 and 4). The ¹¹⁹Sn NMR spectrum confirmed the formation of *n*Bu₃SnCl (δ = 123) and complete disappearance of allyltri-*n*-butyltin (δ = 20). Unfortunately, no actual reacting species has been identified by ¹H NMR spectroscopy, as in the case for allylic titanium.^[1] We observed only the completely demetalated product, propene. Although the actual structure of the tantalum species, whether the allyl ligand is σ- or π-bound, is not clear as yet, the active tantalum species is formed by transmetalation.^[9] In addition to allyltin, benzyl- and alkynyltin compounds also reacted to give benzyl- and alkynyltantalum compounds, respectively (entries 5 and 6, Table 2).

Table 2. Generation of active tantalum reagents “Ta–Nu” according to Scheme 1.^[a]

Entry	Nu	Solvent	<i>n</i> Bu ₃ SnR [equiv]	Yield of <i>n</i> Bu ₃ SnCl [%]
1	allyl	THF	1	99 (16 ^[b])
2	allyl	CH ₃ CN	1	99 (99 ^[b])
3	allyl	CH ₃ CN	2	189
4	allyl	CH ₃ CN	3	250
5	PhCH ₂	CH ₃ CN	2	76
6	PhC≡C	CH ₃ CN	2	83

[a] Yields are from GLC and based on TaCl₅. The reactions were carried out in 1 mL of solvent using TaCl₅ (1 mmol) and allyltin at –40 °C for 30 min. [b] Reaction time of 5 min.

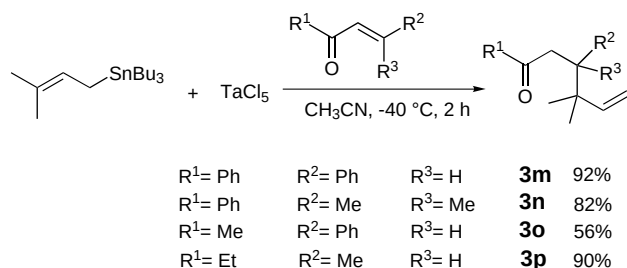
The synthetic advantage of this tin–tantalum system is the stability and easy availability of various tin precursors.^[1, 2] Thus various groups could be introduced to enones by conjugate addition [Eq (1), Table 3]. Methallyltri-*n*-butyltin gave the corresponding adduct **3a** (entry 1, Table 3). When γ-substituted allyltin derivatives were used, the addition occurred at the γ-position selectively to give **3b–3f** (entries 2–6). Besides allylic reagents, benzyltri-*n*-butyltin, alkynyltri-*n*-butyltin derivatives, and α-stannyl esters could be used to give the conjugate adducts **3g–3k**, respectively (entries 7–11). In the case of allenyltri-*n*-butyltin, the β-propargylated adduct **3l** was obtained (entry 12).

Table 3. Conjugate addition of tantalum reagents to enone [Eq (1)].^[a]

$\text{R}^1-\text{C}(\text{O})-\text{CH}=\text{CH}-\text{R}^2 \xrightarrow{\text{“Ta–Nu”}} \text{R}^1-\text{C}(\text{O})-\text{CH}(\text{Nu})-\text{CH}(\text{R}^2)-\text{R}^2$					
Entry	Tin precursor	Enone	Product		Yield [%]
1		1b		3a	54
2		1b		R ¹ , R ² = Ph, Ph 3b	70 ^[b]
3		1f		R ¹ , R ² = Et, Me 3c	79 ^[c]
4		1b		R ¹ , R ² = Ph, Ph 3d	89 ^[d]
5		1f		R ¹ , R ² = Et, Me 3e	97 ^[e]
6		1b		3f	83 ^[f]
7		1b		3g	97
8		1b		R ¹ , R ² = Ph, Ph 3h	76
9		1f		R ¹ , R ² = Et, Me 3i	99
10		1b		3j	57
11		1b		3k	50
12		1b		3l	60

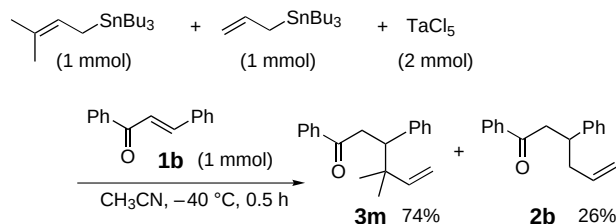
[a] All reactions were carried out in CH₃CN (1 mL) using tin compound (2 mmol), TaCl₅ (1 mmol), and enone **1** (1 mmol) at –40 °C for 2 h. [b] d.r. = 56:44. [c] d.r. = 77:23. [d] d.r. = 82:18. [e] d.r. = 69:31. [f] d.r. = 77:23.

As shown in Scheme 2, even tri-*n*-butylprenyltin effectively gave the corresponding products **3m–3p** in high yields in spite of the bulky *gem*-dimethyl substituents at the γ -position.



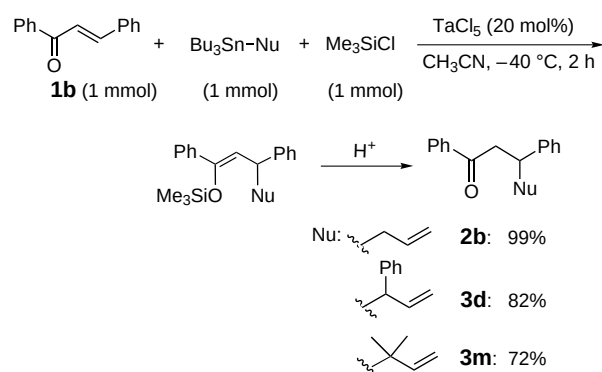
Scheme 2. Conjugate prenylation of enones.

In particular, the product **3n** bearing contiguous quaternary carbon centers could be obtained in 82% yield.^[10] We confirmed that the Sakurai–Hosomi reagent, trimethylprenylsilane/TiCl₄, under the standard conditions^[7] resulted in lower yields of **3n** (11% at –78 °C, 17% at –40 °C). Interestingly, in the competition experiment shown in Scheme 3, more sterically demanding prenyltin reacted predominantly over allyltin to give **3m**.^[11]



Scheme 3. Competition experiment between conjugate prenylation and allylation.

In all cases discussed above, the required molar ratio of TaCl₅ to the allylic tin reagent was 1:2. However, we found that addition of an equimolar amount of trimethylsilyl chloride (Me₃SiCl) enabled the catalytic use of TaCl₅ (Scheme 4). Careful isolation afforded the conjugate adducts as silyl enolates, which were converted to **2b**, **3d**, and **3m** by simple protonolysis. As a tentative catalytic cycle, it can be assumed that the conjugate adduct, tantalum enolate, is



Scheme 4. Catalytic version of the TaCl₅-mediated conjugate addition.

trapped by Me₃SiCl to form silyl enolate along with the regeneration of TaCl₅.

In conclusion, various tantalum reagents could be generated from organotin compounds by transmetalation. In particular, the system described is more broadly applicable on the conjugate allylation of enones than conventional methods.

Experimental Section

Representative procedure of conjugate addition: To a dry nitrogen-filled 10-mL round-bottomed flask containing TaCl₅ (0.358 g, 1 mmol) in MeCN (1 mL) was added allyltri-*n*-butyltin (0.662 g, 2 mmol) at –40 °C. TaCl₅ was partly insoluble. The mixture was stirred at –40 °C for 30 min, before benzalacetone (**1a**) (0.146 g, 1 mmol) was added. As the reaction proceeded, the mixture gradually turned homogeneous and very pale yellow; a drastic change in color was not observed. After the mixture had been stirred at –40 °C for 2 h, MeOH (2 mL) was added and the volatiles were removed under reduced pressure. The residue was chromatographed on a silica-gel column (FL100-DX (Fuji silycia)); eluting with hexane/EtOAc (3/1) gave conjugate adduct **2a** (0.171 g, 91%).

Received: September 24, 2001
Revised: January 21, 2002 [Z17955]

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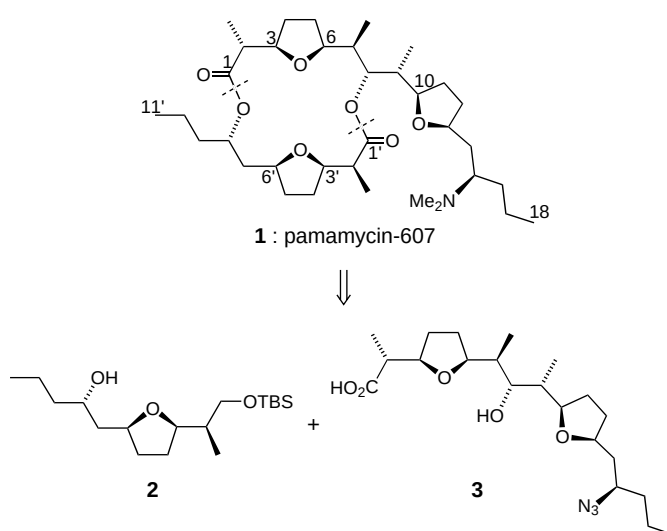
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Total Synthesis of (+)-Pamamycin-607**

Sung Ho Kang,* Joon Won Jeong, Yu Sang Hwang, and Sung Bae Lee

The pamamycins are a novel family of naturally occurring homologous macrodiolides, which are found in *Streptomyces* sp.^[1–9] They induce the aerial mycelium formation in *S. alboniger* to display autoregulatory activity.^[1–3] They also exhibit antibiotic activity against Gram-positive bacteria and pathogenic fungi,^[1,2] inhibit myosin light chain kinase,^[5] and mediate hydrophilic ion transport through lipophilic phases.^[6] In addition, they show vasodilating,^[7] anionophoric,^[2–7] protonophoric,^[8] and autolytic properties.^[9] A major component of the family is pamamycin-607 (**1**), which has a molecular weight of 607. While the structure and relative stereochemistry of pamamycin-607 were elucidated by NMR spectroscopy, its absolute stereochemistry was later determined by a correlation study.^[10] The remarkable biological activity of pamamycin-607 and its unique structural features led us to choose **1** as a synthetic target.^[11] Herein we report an asymmetric total synthesis of **1**.

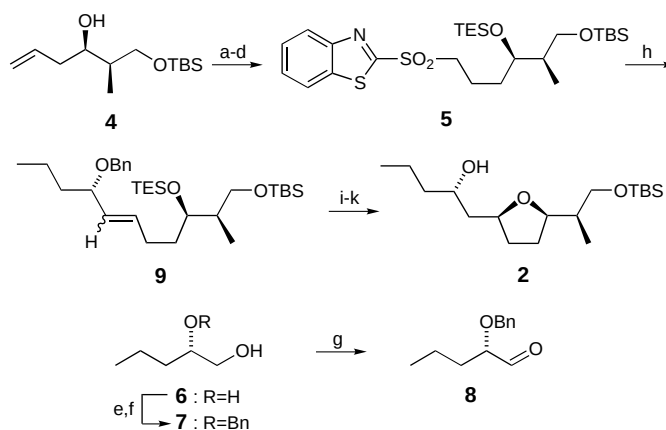
The two ester linkages of **1** were disconnected by retrosynthetic analysis to provide alcohol **2** and carboxylic acid **3** as the precursors of the C1'–C11' and C1–C18 subunits, respectively (Scheme 1). As we envisaged that the three *cis*-2,5-disubstituted tetrahydrofurans comprising **2** and **3** could be formed^[12] by iodoetherification of γ -triethylsilyloxyalkenes, ^[13] **9** (see Scheme 2) and **21** (see Scheme 3) were



Scheme 1.

proposed as the intermediates. Construction of the double bonds in **9** and **21** was planned by means of a sulfone olefination^[14] and the Horner–Emmons reaction. The C2 methyl group could be installed by the cuprate epoxide opening of **23** (see Scheme 4), in which the regioselectivity was assumed to be dictated by the bulky substituent. In addition, while the adjacent hydroxyl and methyl functional groups of **9** were expected to be delivered from the known alcohol **4** (Scheme 2),^[15] those of **21** would be transformed by a Paterson^[16] aldol reaction and Evans *anti* reduction.^[17]

To prepare the bottom subunit **2**, alcohol **4** (78% *de*) was consecutively subjected to silylation, hydroboration, Mitsunobu reaction, and *m*CPBA oxidation to afford sulfone **5** (Scheme 2). The requisite aldehyde **8** (the coupling partner of **5**) was obtained from the known diol **6**^[18] by a sequence of benzylidene formation, DIBAH reduction,^[19] and Swern



Scheme 2. a) TESCl, imidazole, DMF, RT, 83% of desired diastereomer; b) H₃B·SMe₂, THF, RT, then aqueous NaOH, H₂O₂, RT, 85%; c) Ph₃P, 2-mercaptobenzothiazole, DEAD, THF, 0°C→RT, 87%; d) *m*CPBA, CH₂Cl₂, RT, 90%; e) TsOH, PhCHO, PhMe, reflux (–H₂O), 94%; f) DIBAH, PhMe, 0°C, 88% for **7**; g) Swern oxidation; h) LiHMDS, THF, –78°C, then **8**, RT, 80%; i) I₂, Ag₂CO₃, Et₂O, RT, 92%; j) Ph₃SnH, Et₃B, THF, 0°C, 90%; k) H₂, 10% Pd/C, MeOH, RT, 99%. TES = triethylsilyl, DMF = N,N-dimethylformamide, DEAD = diethyl azodicarboxylate, *m*CPBA = 3-chloroperoxybenzoic acid, Ts = toluenesulfonyl, DIBAH = diisobutylaluminum hydride, LiHMDS = lithium bis(trimethylsilyl)amide.

[*] Prof. Dr. S. H. Kang, J. W. Jeong, Yu. S. Hwang, S. B. Lee
Center for Molecular Design and Synthesis
Department of Chemistry, School of Molecular Science
Korea Advanced Institute of Science and Technology, Taejeon 305-701 (Korea)
Fax: (+82)42-869-2810
E-mail: shkang@kaist.ac.kr

[**] This work was supported by C.M.D.S. and the Brain Korea 21 Project.

oxidation.^[20] Addition of **8** to the lithium anion obtained from **5** provided a 1.2:1 mixture of *trans*- and *cis*-alkenes **9**. After several strategic model studies we chose the iodoetherification of γ -triethylsilyloxyalkenes, because our total synthesis required the development of reliable methodology to form *cis*-2,5-disubstituted tetrahydrofurans. Experimental optimization revealed that the most efficient outcome could be attained by exposing **9** to iodine in the presence of silver carbonate in diethyl ether. The iodocyclization of both the *cis* and *trans* isomers proceeded with similar efficiency (since the isomers were inseparable, the 1.2:1 mixture of *trans*- and *cis*-alkenes **9** was subjected to iodoetherification to provide a 1.2:1 mixture of iodides in 92% yield). It is of note that the addition of silver carbonate was unprecedented, to our knowledge, and indispensable for the consistency, stereoselectivity, and completion of the iodocyclization. Remarkably, reductive deiodination^[21] and debenzoylation of the cyclized products gave rise to **2** as the only stereoisomer.

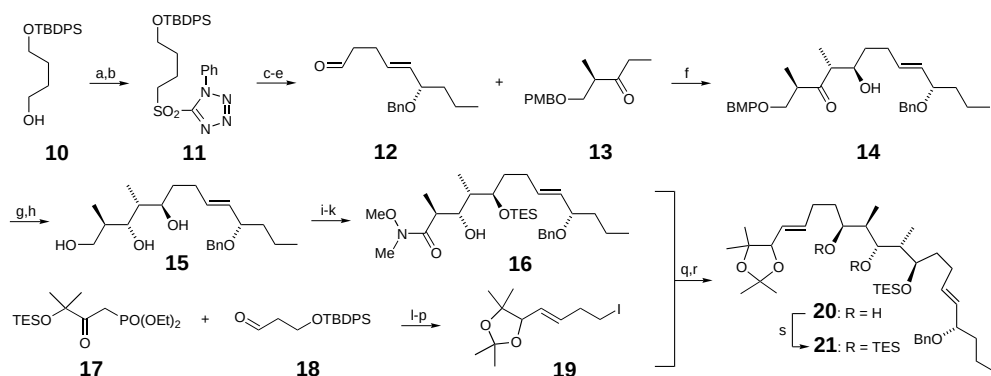
Once the assembly of the C1'–C11' subunit was complete, the synthesis of the upper subunit **3** began with the formation of sulfone **11**, derived from alcohol **10**^[22] by Mitsunobu reaction and *m*CPBA oxidation (Scheme 3). The coupling of **11** with **8** using KHMDS, and the ensuing desilylation, produced a 7:1 separable mixture of *trans*- and *cis*-alkenes. Although the mixture could be employed for the next synthetic sequence, the *trans* and *cis* isomers were separated for the purposes of spectroscopic interpretation in the following steps, and then the *trans*-olefinic alcohol was oxidized to aldehyde **12**.

Aldol condensation of the known ethylketone **13**^[23] with **12** occurred via an *E*-boron enolate to provide a 31:1 mixture of the desired *anti*-aldol product **14** and the corresponding diastereomers. Stereoselective *anti* reduction of the keto group of **14** and the subsequent deprotection gave predominantly the desired α -alcohol **15**, along with a small amount of the isomeric β -alcohol (>60:1). Alcohol **15** was chemoselectively oxidized^[24] to a six-membered lactone, which was subjected to Weinreb-amide formation^[25] and regioselective monosilylation to yield the Weinreb amide **16**.

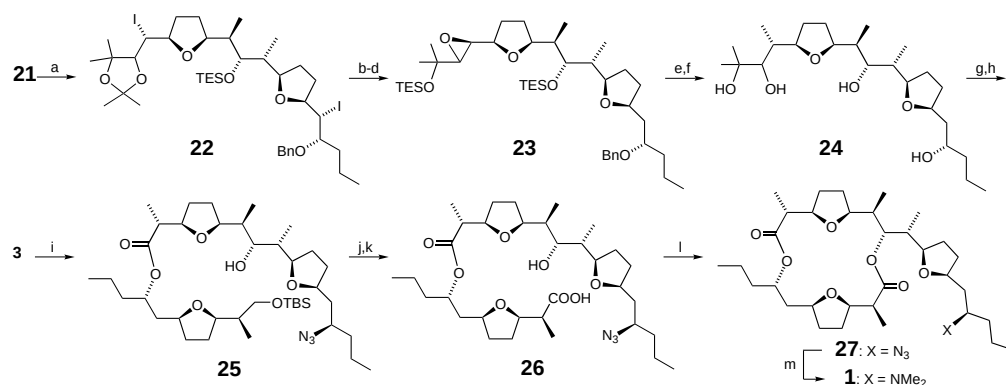
With access to the right part of **21** secure, it was necessary to prepare its left part as alkyl iodide. Accordingly, the known phosphonate **17**^[26] was olefinated with aldehyde **18** to furnish exclusively the *trans*-alkene. The conjugated ketone was reduced,^[27] desilylated, protected as the acetamide, and iodinated to give the racemic iodide **19**. Transmetalation of **19** followed by the addition of amide **16** yielded the β -hydroxyketone. Diastereoselective *anti* reduction of the ketone gave a 20:1 mixture of the desired stereoisomeric alcohols **20** and their corresponding diastereomers. After disilylation of **20**, double iodoetherification of the generated silyl ethers **21** was performed under the aforementioned cyclization conditions to supply tetrahydrofurans **22** with complete *cis* stereoselectivity. Derivatization of **22** to form epoxide **23** was achieved by successive acidic deprotection, cyclization, reductive deiodination, and silylation (Scheme 4). Methylation of **23** with lithium dimethylcuprate yielded only the desired regioisomeric alcohols, with partially desilylated secondary silyloxy groups. Hydrogenation of the mixture removed the benzyl and triethylsilyl groups concurrently. The produced tetraols **24** were subjected to Mitsunobu conditions,^[28] to convert the least hindered hydroxyl group into an azido group chemoselectively. The resulting vicinal diols were oxidized to give carboxylic acid **3**.

With the synthesis of the two key subunits **2** and **3** completed, these units were coupled under Yamaguchi's conditions,^[29] and the coupled ester **25** was desilylated, and subsequently oxidized chemoselectively to carboxylic acid **26**.^[30] Lactonization of **26** via the thiopyridyl ester, in the presence of cupric bromide,^[31] gave macrodilide **27**. The azido group of **27** was reduced and the in situ addition of formaldehyde to the generated amine under the hydrogenation conditions produced pamamycin-607 (**1**). The synthetic **1** and its CF₃COOD salt were identical to the natural pamamycin-607 and its CF₃COOD salt in all aspects.^[10a, 32]

A highly enantioselective total synthesis of pamamycin-607 has been attained from the readily available alcohol **10** through 27 steps (5.4% overall yield). The synthetic sequence culminated in a stereoselective double cyclization in the



Scheme 3. a) 1-Phenyl-1H-tetrazole-5-thiol, Ph₃P, DEAD, THF, RT, 86%; b) *m*CPBA, NaHCO₃, CH₂Cl₂, RT, 93%; c) KHMDS, **8**, DME, –78 °C → RT; d) *n*Bu₄NF, THF, RT, 72% for *trans* isomer and 2 steps; e) Swern oxidation; f) **13**, cHx₂BCl, Et₃N, Et₂O, 0 °C, then **12**, –78 → –20 °C, 85%; g) Me₄NBH(OAc)₃, AcOH, MeCN, –30 → –20 °C, 88%; h) (NH₄)₂Ce(NO₃)₆, H₂O, MeCN, 0 °C, 88%; i) TEMPO, NCS, *n*Bu₄NCl, aq. NaHCO₃, K₂CO₃ (pH 8.6), CH₂Cl₂, RT, 97%; j) MeONHMe · HCl, Me₃Al, CH₂Cl₂, –78 °C, 92%; k) TESCl, imidazole, CH₂Cl₂, –40 °C, 99%; l) *i*Pr₂NEt, LiCl, MeCN, RT, 88%; m) NaBH₄, CeCl₃ · 7H₂O, MeOH, 0 °C, 96%; n) *n*Bu₄NF, THF, RT, 99%; o) *p*-TsOH, acetone, RT, 92%; p) I₂, Ph₃P, imidazole, THF, 0 °C → RT, 96%; q) *t*BuLi, Et₂O, –78 → –20 °C, then **16**, –50 → –20 °C, 82%; r) Me₄NBH(OAc)₃, AcOH, MeCN, –20 °C, 92%; s) TESOTf, Et₃N, CH₂Cl₂, 0 °C, 98%. KHMDS = potassium bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane, cHx = cyclohexyl, Ac = acetyl, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, NCS = N-chlorosuccinimide, OTf = trifluoromethanesulfonate.



Scheme 4. a) I_2 , Ag_2CO_3 , Et_2O , RT, 81 %; b) 2 N HCl, MeOH, reflux, then K_2CO_3 , RT, 86 %; c) Ph_3SnH , Et_3B , THF, 0 °C, 96 %; d) TESOTf, Et_3N , CH_2Cl_2 , –20 °C, 89 %; e) Me_2CuLi , Et_2O , 5 °C; f) H_2 , $Pd(OH)_2/C$, $EtOH$, RT, 88 % for 2 steps; g) HN_3 , Ph_3P , DEAD, PhH , 0 °C, 97 %; h) $NaIO_4$, $tBuOH$, H_2O , RT, then 1.25 M NaH_2PO_4 , 1 M $KMnO_4$, RT, 87 %; i) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, RT, then 2, DMAP, PhH , RT, 90 %; j) nBu_4NF , THF, RT, 94 %; k) TEMPO, $NaClO_2$, NaH_2PO_4 buffer (pH 6.7), NaOCl, MeCN, RT, 91 %; l) $(PyS)_2$, Ph_3P , MeCN, then $CuBr_2$, MeCN, RT, 62 %; m) H_2 , 10 % Pd/C, MeOH, RT, then 37 % aq. HCHO, AcOH, RT, 89 %. DMAP = 4-dimethylaminopyridine, $(PyS)_2$ = 2,2'-dipyridyl disulfide.

presence of the unprecedented additive silver carbonate, and the sterically controlled, regioselective cuprate epoxide opening.

Experimental Section

22: Silver carbonate (970 mg, 3.50 mmol) was stirred with iodine (1.23 g, 8.76 mmol) in Et_2O (15 mL) at room temperature for 5 min. The heterogeneous solution was cooled to 0 °C and then **21** (390 mg, 0.438 mmol) dissolved in Et_2O (4 mL) was added. The resulting solution was warmed to room temperature immediately and stirred for 15 h. After quenching with aqueous $Na_2S_2O_3$ (10 %, 30 mL), the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and the solvent evaporated in vacuo. The residue was purified by flash chromatography (SiO_2 , $EtOAc$:hexane 1:30) to give **22** (323 mg, 81 %).

1: ^1H NMR (400 MHz, $CDCl_3$): δ = 4.88 (1H, dd, J = 10.8, 0.6 Hz), 4.82 (1H, dddd, J = 11.4, 6.6, 4.8, 4.0 Hz), 4.15 (1H, ddd, J = 8.6, 5.5, 2.2 Hz), 4.01 (1H, td, J = 9.5, 5.0 Hz), 3.95 (1H, ddd, J = 9.0, 6.9, 2.2 Hz), 3.86 (1H, br t, J = 8.5 Hz), 3.77–3.71 (1H, m), 3.60 (1H, td, J = 10.2, 3.9 Hz), 3.34 (1H, dt, J = 10.0, 6.7 Hz), 3.12 (3H, d, J = 5.2 Hz), 2.82 (3H, d, J = 5.0 Hz), 2.58 (1H, qd, J = 6.9, 2.2 Hz), 2.24–1.12 (27H, m), 1.05 (3H, d, J = 7.0 Hz), 1.04 (3H, d, J = 6.8 Hz), 0.97 (3H, t, J = 7.1 Hz), 0.86 (3H, t, J = 7.3 Hz), 0.77 (3H, d, J = 6.6 Hz), 0.77 (3H, d, J = 6.9 Hz); the protons adjacent to that at 4.82 ppm appear at 2.24–1.12 ppm (27H, m), the other J = 11.4 Hz coupling is buried in this region. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 173.2, 82.2, 80.2, 78.5, 78.3, 76.4, 74.5, 74.4, 71.1, 66.9, 47.2, 43.0, 41.4, 41.0, 38.6, 37.4, 37.0, 36.9, 34.3, 31.5, 31.1, 30.5, 29.6, 29.5, 27.6, 27.3, 19.5, 18.0, 14.1 (2 peaks), 13.8, 10.3, 9.6, 8.7; IR (neat): ν 2966, 2875, 1737, 1466, 1385, 1265, 1189, 1127, 1112, 1071, 1054 cm^{-1} ; HRMS (EI) calcd for $C_{35}H_{61}NO_7$: 607.4448, found: 607.4447; ($[\alpha]_D^{20}$) = +10.9, c = 0.30, MeOH), ($[\alpha]_D^{25}$) = +21.7, c = 0.30, MeOH), ($[\alpha]_D^{32}$) = +23.0, c = 0.30, MeOH).

1·D⁺CF₃COO[−]: The synthetic **1** (7 mg, 0.0115 mmol) was dissolved in $[D_6]$ acetone (0.5 mL) in the presence of CF_3COOD (5 μ L, 0.0649 mmol) in a glove box. This solution was sampled for NMR spectral analysis. ^1H NMR (400 MHz, $[D_6]$ acetone): δ = 4.99 (1H, dd, J = 11.0, 0.8 Hz), 4.92 (1H, dddd, J = 11.8, 6.7, 5.1, 3.8 Hz), 4.28 (1H, ddd, J = 9.0, 5.6, 2.3 Hz), 4.09 (1H, ddd, J = 9.1, 6.9, 2.2 Hz), 3.92–3.81 (2H, m), 3.71 (1H, ddd, J = 10.8, 9.9, 4.0 Hz), 3.66–3.59 (1H, m), 3.41–3.34 (1H, m), 3.23 (3H, s), 2.98 (3H, s), 2.74 (1H, dq, J = 6.8, 2.2 Hz), 2.26 (1H, dq, J = 10.2, 7.0 Hz), 2.31–2.26 (1H, m), 2.09–1.10 (25H, m), 1.09 (3H, d, J = 7.0 Hz), 1.05 (3H, d, J = 6.8 Hz), 1.00 (3H, t, J = 7.2 Hz), 0.87 (3H, t, J = 7.3 Hz), 0.85 (6H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $[D_6]$ acetone): δ = 175.0, 173.8, 83.2, 81.1, 80.0, 79.3, 77.3, 75.3, 75.2, 71.5, 68.7, 47.9, 43.8, 42.1, 41.6, 39.5, 37.9 (2 peaks), 36.6, 34.3, 32.1, 31.6, 31.2, 30.1, 29.0, 28.1, 28.0, 20.4, 18.8, 14.3, 14.1, 14.0, 10.4, 9.8, 8.7.

Received: December 19, 2001 [Z18413]

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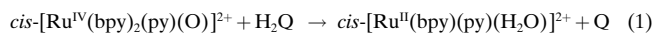
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Proton-Coupled Electron Transfer from Phosphorus: A P–H/P–D Kinetic Isotope Effect of 178**

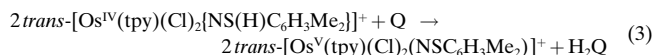
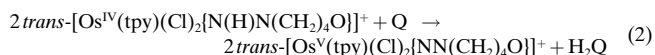
My Hang V. Huynh* and Thomas J. Meyer*

In the extensive redox chemistry of high oxidation state ruthenium(IV)–oxo,^[1] osmium(VI)–nitrido,^[2] osmium(IV–VI)–hydrazido,^[3] osmium(IV)–cyanoimido,^[4] and osmium(IV)–

sulfilimido complexes,^[5] multiple mechanistic pathways have been uncovered based on multiple electron and atom/group transfers. Examples include O atom,^[6] N[–] ion,^[7] H[–] ion,^[8] and NSC₆H₃Me₂^{2–} transfer.^[9] Kinetic studies have revealed the existence of proton-coupled electron-transfer pathways based on bound oxo/hydroxo/aqua,^[1, 10] dialkylhydrazido,^[11] and sulfilimido^[12] ligands that occur with large H/D kinetic isotope effects. Examples include $k_{\text{O-H}}/k_{\text{O-D}} = 30 \pm 1$ ^[10a] for the oxidation of hydroquinone (H₂Q) to benzoquinone (Q) by *cis*-[Ru^{IV}(bpy)₂(py)(O)]²⁺ (bpy = 2,2'-bipyridine and py = pyridine) [Eq. (1)].

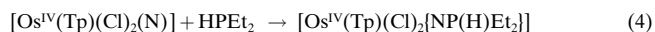


Other examples are $k_{\text{N-H}}/k_{\text{N-D}} \geq 41.4 \pm 1.3$ ^[11] for the reduction of Q to H₂Q by *trans*-[Os^{IV}(tpy)(Cl)₂N(H)N(CH₂)₄O]]⁺ [Eq. (2); tpy = 2,2':6',2''-terpyridine], and $k_{\text{S-H}}/k_{\text{S-D}} \geq 31.1 \pm 0.2$ ^[12] for the oxidation of *trans*-[Os^{IV}(tpy)(Cl)₂NS(H)-C₆H₃Me₂]]⁺ by Q [Eq. (3)].

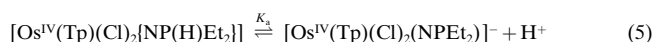


We report here the first example of proton-coupled electron transfer based on a phosphorus atom. Its existence may have important implications for the redox reactivity of organophosphorus compounds,^[13] phosphoraniminato complexes,^[14] and biologically active substances containing P–H acids.^[15]

A rapid reaction occurs between the osmium(VI)–nitrido complex, [Os^{VI}(Tp)(Cl)₂(N)] (Tp[–] = tris(pyrazolyl)borate), and diethylphosphane (HPET₂) in CH₂Cl₂ under nitrogen at room temperature to give the osmium(IV)–phosphoraniminato product, [Os^{IV}(Tp)(Cl)₂[NP(H)Et₂]] (Os^{IV}NP(H)Et₂) [Eq. (4)].



The product was isolated (94 % yield) and characterized by elemental analysis,^[16a] cyclic voltammetry,^[16b] and UV/Vis,^[16c] and infrared^[16d] spectroscopies. Similar to other d⁴ Os^{IV}–phosphoraniminato complexes,^[17] Os^{IV}–NP(H)Et₂ is paramagnetic as shown by ¹H NMR spectroscopy. Cyclic voltammetric measurements in 1:1 (v/v) CH₃CN:H₂O ($\mu = 1.0$ M in NH₄PF₆) reveal that $E_{1/2}$ for the osmium(VI/IV) couple decreases by 57 mV/pH unit from pH 0 ($E_{1/2} = 0.560$ V, versus sodium saturated calomel electrode (SSCE)) to 3.5 ($E_{1/2} = 0.360$ V, versus SSCE) and is pH independent above pH 3.5.^[18] From these data, $\text{p}K_{\text{a}} = 3.52 \pm 0.04$ for the acid–base equilibrium shown in Equation (5), and Supporting Information Figure 1.



Reminiscent of the [Os^V(tpy)(Cl)₂{NN(CH₂)₄O}]]⁺/[Os^{IV}(tpy)(Cl)₂[N(H)N(CH₂)₄O]]⁺ and [Os^V(tpy)(Cl)₂–(NSC₆H₃Me₂)]⁺/[Os^{IV}(tpy)(Cl)₂NS(H)C₆H₃Me₂]]⁺ couples,

[*] Dr. T. J. Meyer
Associate Laboratory Director for Strategic Research
Los Alamos National Laboratory, MS A127
Los Alamos, NM 87545 (USA)
Fax: (+1) 505-667-5450
E-mail: tjmeyer@lanl.gov

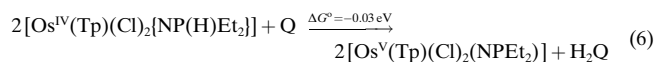
Dr. M. H. V. Huynh
Director-Funded Postdoctoral Fellow
Los Alamos National Laboratory, Chemistry Division MS J514
Los Alamos, NM 87545 (USA)
Fax: (+1) 505-667-9905
E-mail: huynh@lanl.gov

[**] We are grateful to the Laboratory Directed Research and Development Program for support of this research. M.H.V.H. gratefully acknowledges postdoctoral fellowship support from the Director's Office of Los Alamos National Laboratory. Los Alamos National Laboratory is operated by the University of California for the U.S. Department of Energy under Contract W-7405-ENG-36.

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

we have found clear kinetic evidence for proton-coupled electron transfer based on phosphorus for the $[\text{Os}^{\text{V}}(\text{Tp})(\text{Cl})_2(\text{NPEt}_2)]/[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ couple.

When $[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ and Q are mixed in 1:1 (v/v) $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (pH 1.5 and $\mu = 1.0\text{ M}$ in NH_4PF_6), a rapid reaction occurs in which Q is reduced to H_2Q , and $[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ is oxidized to $[\text{Os}^{\text{V}}(\text{Tp})(\text{Cl})_2(\text{NPEt}_2)]$ [Eq. (6)]. From redox potential measurements, $\Delta G^\circ = -0.03\text{ eV}$ for this reaction.^[18]



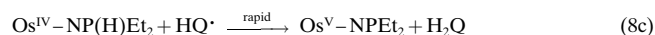
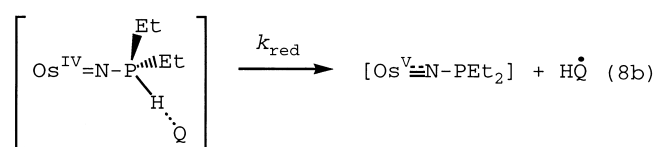
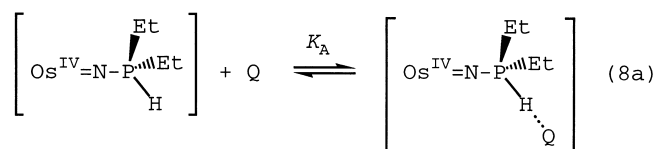
As found for the oxidation of *trans*- $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})_2(\text{N}(\text{H})\text{N}(\text{CH}_2)_4\text{O})]^+$ and *trans*- $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})_2(\text{NS}(\text{H})\text{ArMe}_2)]^+$ by Q, the oxidation of $[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ by Q is pH dependent, consistent with the rate law in Equations (7a) and (7b) at $[\text{Q}] < 3.05 \times 10^{-3}\text{ M}$ with $k_1(\text{H}_2\text{O}) = (1.48 \pm 0.01) \times 10^4\text{ M}^{-1}\text{ s}^{-1}$, $k_2(\text{H}_2\text{O}) = (3.95 \pm 0.04) \times 10^2\text{ M}^{-1}\text{ s}^{-1}$, and $K_a = 3.2 \times 10^{-4}$. This rate law is consistent with competing pathways, and the oxidation of $\text{Os}^{\text{IV}}-\text{NP}(\text{H})\text{Et}_2$ (k_1) and of $\text{Os}^{\text{IV}}-\text{NPEt}_2^-$ (k_2) by Q.

$$\text{Rate} = k_{\text{obs}}[\text{Q}][\text{Os}^{\text{IV}}]_{\text{T}} \quad (7a)$$

$$k_{\text{obs}} = \left\{ \frac{2k_1[\text{H}^+] + 2k_2K_a}{[\text{H}^+] + K_a} \right\} \quad (7b)$$

As in the reaction between *trans*- $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})_2(\text{N}(\text{H})\text{N}(\text{CH}_2)_4\text{O})]^+$ and Q, there is evidence in the k_1 pathway for an $\text{Os}^{\text{IV}}-\text{NP}(\text{H})\text{Et}_2 \cdots \text{Q}$ intermediate. This conclusion is based on the appearance of saturation kinetics in $[\text{Q}]$ (Figure 1) and by the direct observation of the intermediate. At $[\text{Q}] = 1.2 \times 10^{-3} - 1.2 \times 10^{-2}\text{ M}$, a shift occurs in the characteristic λ_{max} for $\text{Os}^{\text{IV}}-\text{NP}(\text{H})\text{Et}_2$ in $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ at pH 1.5 from 366 nm to 382 nm. This feature subsequently disappears to give the spectrum of $[\text{Os}^{\text{V}}(\text{Tp})(\text{Cl})_2(\text{NPEt}_2)]$ with $\lambda_{\text{max}} = 396\text{ nm}$.

These observations and that the reaction is dominated ($\sim 80\%$) at pH 1.5 by the k_1 pathway are consistent with the mechanism in Equations (8a)–(8c). Related mechanisms involving pre-association with formation of H-bonded adducts have been found in the oxidations of *trans*- $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})_2(\text{N}(\text{H})\text{N}(\text{CH}_2)_4\text{O})]\text{PF}_6^{[11]}$ and *trans*- $[\text{Os}^{\text{IV}}(\text{tpy})(\text{Cl})_2(\text{NS}(\text{H})\text{C}_6\text{H}_3\text{Me}_2)]\text{PF}_6^{[12]}$ by Q.



From the plots of k_{obs} versus $[\text{Q}]$ and of $1/k_{\text{obs}}$ versus $1/[\text{Q}]$ (Figure 1) k_{red} in H_2O is $(1.54 \pm 0.02) \times 10^{-2}\text{ s}^{-1}$, and $K_a(\text{H}_2\text{O})$ is $(2.15 \pm 0.02) \times 10^3\text{ M}^{-1}$.

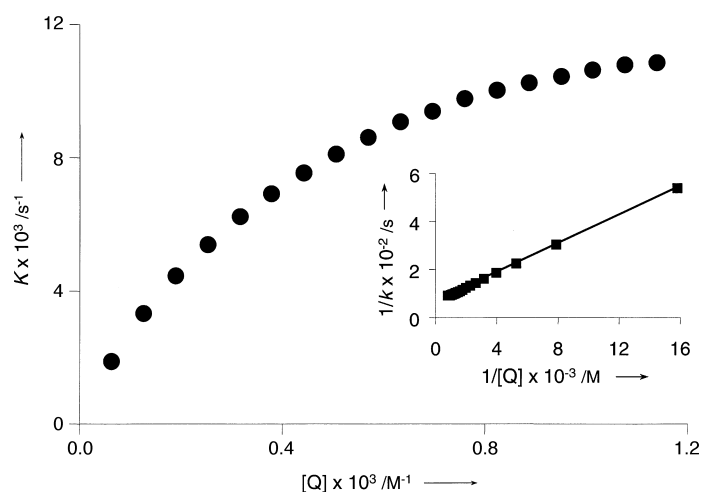


Figure 1. Plot of k_{obs} versus $[\text{Q}]$ for the reaction between Q and $[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ in 1:1 (v/v) $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ ($25.0 \pm 0.1^\circ\text{C}$, $[\text{H}^+] = 3.2 \times 10^{-2}\text{ M}$, and $\mu = 1.0\text{ M}$ in NH_4PF_6). A plot of $1/k_{\text{obs}}$ versus $1/[\text{Q}]$ is shown in the inset.

The pH-dependent experiments were repeated from pH 0.0–2.5 ($\mu = 1.0\text{ M}$ in NH_4PF_6) in 1:1 (v/v) $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ and 1:1 (v/v) $\text{CH}_3\text{CN}:\text{D}_2\text{O}$ at $25.0 \pm 0.1^\circ\text{C}$ at relatively low $[\text{Q}]$ ($\leq 3.04 \times 10^{-3}\text{ M}$) under conditions where the k_1 pathway is first order in $[\text{Q}]$. At these conditions, $[\text{H}^+]$ is much larger than K_a , and it follows from Equation (7b) that K_{obs} is given by Equation (9).

$$k_{\text{obs}} = 2k_1 + \frac{2k_2K_a}{[\text{H}^+]} \quad (9)$$

From the plots of k_{obs} versus $1/[\text{H}^+]$ in Figure 2, $k_1(\text{H}_2\text{O}) = (1.48 \pm 0.01) \times 10^4\text{ M}^{-1}\text{ s}^{-1}$ and $k_2(\text{H}_2\text{O}) = (3.95 \pm 0.04) \times 10^2\text{ M}^{-1}\text{ s}^{-1}$ and $k_1(\text{D}_2\text{O}) = (8.30 \pm 0.07) \times 10^{-2}\text{ M}^{-1}\text{ s}^{-1}$ and $k_2(\text{D}_2\text{O}) = (1.16 \pm 0.01) \times 10^2\text{ M}^{-1}\text{ s}^{-1}$. Based on these data, $k_1(\text{H}_2\text{O})/k_1(\text{D}_2\text{O}) = 178.3 \pm 7.5$ and $k_2(\text{H}_2\text{O})/k_2(\text{D}_2\text{O}) = 3.41 \pm 0.01$.

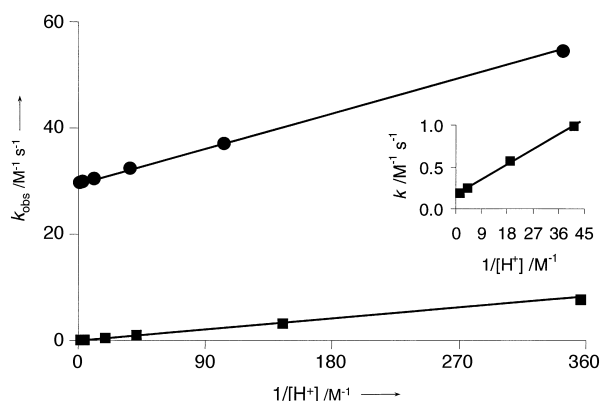


Figure 2. pH dependence of k_{obs} for the reaction between $[\text{Os}^{\text{IV}}(\text{Tp})(\text{Cl})_2(\text{NP}(\text{H})\text{Et}_2)]$ and Q from pH 0.0 to 2.5 in 1:1 (v/v) $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ ($\mu = 1.0\text{ M}$ in NH_4PF_6) at $T = 25.0 \pm 0.1^\circ\text{C}$ and $\text{CH}_3\text{CN}:\text{D}_2\text{O}$. A plot of the same reaction under the same conditions in $\text{CH}_3\text{CN}:\text{D}_2\text{O}$ from pH 0.0 to 1.6 is shown in the inset.

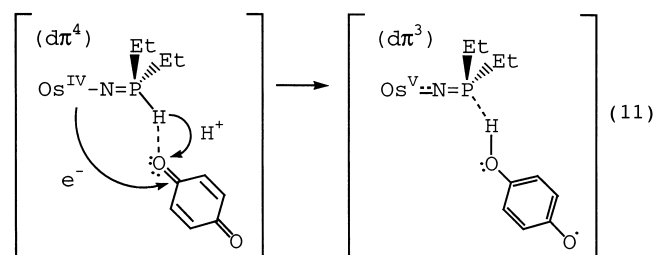
The observation of a kinetic isotope effect of 178.3 ± 7.5 for k_1 is remarkable. Given the mechanism in Equations (8a) and (8b), k_1 is the product $k_{\text{red}}K_A$. A series of experiments was conducted at pH = 1.5 (pD = 1.1) at high concentration of Q, up to 1.46×10^{-3} M. Under these conditions, saturation kinetics in [Q] were observed for the k_1 pathway, consistent with the rate law in Equations (10a) and (10b).

$$\text{Rate} = k_{\text{obs}}[\text{Os}^{\text{IV}}]_{\text{T}} \quad (10a)$$

$$k_{\text{obs}} = \frac{k_{\text{red}}K_A[\text{Q}] + k_2\frac{K_A}{[\text{H}^+]}[\text{Q}]}{K_A[\text{Q}] + 1} \quad (10b)$$

From plots of $1/k_{\text{obs}}$ versus $1/[\text{Q}]$ (Supporting Information Figure 2), $K_A(\text{D}_2\text{O}) = (2.10 \pm 0.02) \times 10^3 \text{ M}^{-1}$ and $k_{\text{red}}(\text{D}_2\text{O}) = (1.96 \pm 0.03) \times 10^{-4} \text{ s}^{-1}$. Based on this result, $K_A(\text{H}_2\text{O})/K_A(\text{D}_2\text{O}) = 1.02 \pm 0.02$ and $k_{\text{red}}(\text{H}_2\text{O})/k_{\text{red}}(\text{D}_2\text{O}) = 175.1 \pm 0.9$. This fact shows that the isotope effect appears largely in the redox step, k_{red} , and the large isotope effect points to a proton-coupled electron-transfer mechanism.

As shown in Equation (11), proton-coupled electron transfer in this case involves $d\pi(\text{Os}^{\text{IV}}) \rightarrow n\pi^*(\text{Q})$ electron transfer coupled to $\text{sp}^3(\text{P}) \rightarrow \text{sp}^2(\text{O})$ proton transfer from the Os^{IV} donor to the benzoquinone acceptor.



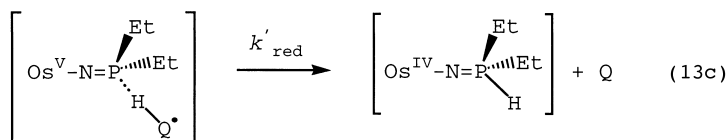
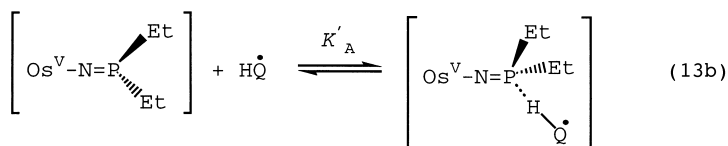
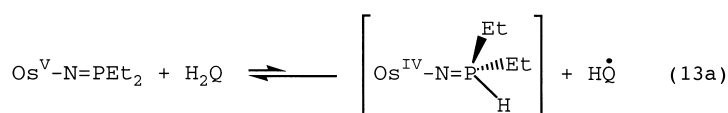
Hydrogen-atom transfer with both electron and proton transferred from $\text{sp}^3(\text{P}-\text{H})$ would lead to the high energy, ligand-oxidized intermediate, $\text{Os}^{\text{IV}}-\text{NP}^+\text{Et}_2$.

The magnitude of the kinetic isotope effect points to the importance of tunneling and a large tunneling distance which occurs by the coupling of a $\nu(\text{P}-\text{H})$ mode in the donor and a $\nu(\text{O}-\text{H})$ mode in the $\text{HQ}^\bullet$ product.

The driving force for the reaction in Equation (6) is -0.03 eV , and the reaction is measurably reversible.^[19] The results of an initial kinetic study on the oxidation of H_2Q by $[\text{Os}^{\text{V}}(\text{Tp})(\text{Cl})_2(\text{NPEt}_2)]$ reveal the rate law shown in Equation (12).

$$\frac{-d[\text{Os}^{\text{V}}]}{dt} = k_{\text{obs}} \frac{[\text{Os}^{\text{V}}-\text{NPEt}_2]^2[\text{H}_2\text{Q}]}{[\text{Os}^{\text{IV}}-\text{NP}(\text{H})\text{Et}_2]} \quad (12)$$

This result is consistent with the reverse of the mechanism in Equations (8a)–(8c) and rate-limiting proton-coupled electron transfer between $\text{HQ}^\bullet$ and $\text{Os}^{\text{V}}-\text{NPEt}_2$. The initial reaction between H_2Q and $\text{Os}^{\text{V}}-\text{NPEt}_2$ is a rapid pre-equilibrium. Initial results at high $[\text{H}_2\text{Q}]$ have provided direct evidence for the intermediate, $\text{Os}^{\text{V}}-\text{NPEt}_2 \cdots \text{HQ}^\bullet$, and the mechanism for the reverse reaction shown in Equations (13a)–(13c).



In conclusion, our study provides the first documented example of proton-coupled electron transfer involving a phosphorus atom that is not directly bonded to a metal. The large magnitude of the kinetic isotope effect is also remarkable and opens the possibility of observing giant isotope effects in related reactions where proton-coupled electron transfer is the dominant mechanism.

Received: November 8, 2001

Revised: January 21, 2002 [Z 18185]

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A New Crystal Modification of Chromium Tetrafluoride: $\beta\text{-CrF}_4^{**}$

Primož Benkič, Zoran Mazej,* and Boris Žemva

In memoriam Karel Lutar

Part of the investigations into reactions between chromium fluorides (CrF_2 , CrF_3 , CrF_5) and xenon fluorides (XeF_2 , XeF_6) was a search for appropriate starting materials for the preparation of pure solid CrF_4 .^[1,2] It was found that solid $\text{XeF}_2 \cdot \text{CrF}_4$ is quickly solvolyzed in anhydrous hydrogen fluoride (aHF) to give amethyst CrF_4 .^[1] Although the obtained CrF_4 was of very low crystallinity, its X-ray powder diffraction pattern indicated that it has a different crystal structure than CrF_4 prepared by direct fluorination of elemental chromium with an aHF/ F_2 mixture at 573 K.^[3]

[*] Dr. Z. Mazej, Dipl.-Chem. P. Benkič, Prof. Dr. B. Žemva
Jožef Stefan Institute
Jamova 39, SI-1000 Ljubljana (Slovenia)
Fax: (+386) 1-423-2125
E-mail: zoran.mazej@ijs.si

[**] The authors gratefully acknowledge the financial support of the Ministry of Education, Science and Sport of the Republic of Slovenia.

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

However, efforts to prepare single crystals of the new form of CrF_4 were plagued by the same preparative difficulties that prevent the growth of suitable single crystals of higher binary fluorides (high reactivity, moisture sensitivity, tendency to disproportionate, and thermal decomposition to lower valent compounds and elemental fluorine). Because of their reactivity they can be handled only in a few solvents, and their low solubility makes the preparation of single crystals from saturated solutions infeasible. For these reasons the preparation of single crystals of each 3d transition metal tetrafluoride represented a special challenge, and different preparation conditions were required in each case. We found that slow thermal decomposition of CrF_5 at 403 K yields large, beautiful, dark red-violet single crystals. Their color, vibrational data (see Supporting Information), and chemical analysis (see Experimental Section) confirmed that single crystals of CrF_4 were obtained. The presence of lower chromium fluorides (CrF_2 , Cr_2F_5 , or CrF_3) or oxyfluorides (CrF_2O , CrF_3O , CrF_4O , or CrF_2O_2) was excluded.

The crystal structures of the lower chromium fluorides (CrF_2 ,^[4] Cr_2F_5 ,^[5] CrF_3)^[6] have long been known, and the crystal structure of CrF_4 was reported recently.^[3] Here we report on a new crystal modification of CrF_4 , which we named $\beta\text{-CrF}_4$ to distinguish it from the already known $\alpha\text{-CrF}_4$.^[3]

The tetrafluorides MF_4 can be divided into five groups. The first group contains MF_4 of larger M^{4+} ions ($\text{M} = \text{Hf}$, Ce , Pr , Tb , Th – Bk),^[7] isostructural to $\beta\text{-ZrF}_4$,^[7] the second the structurally related MF_4 ($\text{M} = \text{Rh}$, Os , Ir , Pt , Pd , Re),^[8,9] the third the structurally related NbF_4 ,^[10,11] SnF_4 ,^[12] PbF_4 ,^[12] VF_4 ,^[10] and RuF_4 ,^[11] and the fourth SeF_4 and TeF_4 .^[13] The fifth group includes TiF_4 ,^[14] $\alpha\text{-MnF}_4$,^[15] $\beta\text{-MnF}_4$,^[15] $\alpha\text{-ZrF}_4$,^[16] and $\alpha\text{-CrF}_4$,^[3] which represents unique examples. $\beta\text{-CrF}_4$ crystallizes in a new structural type. The basic unit of the crystal structure consists of four corner-sharing CrF_6 octahedra (Figure 1). Tetrameric rings are thus formed in which four Cr atoms are connected by *cis* bridging fluorine atoms. The coordination sphere around Cr atoms is completed by two *cis* terminal fluorine atoms and two *trans* bridging fluorine atoms

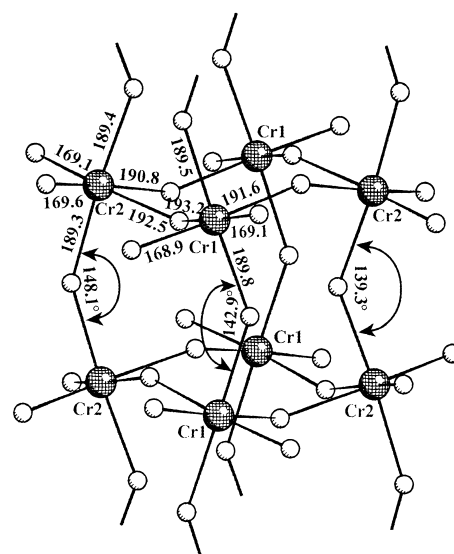


Figure 1. Section of the crystalline structure of $\beta\text{-CrF}_4$ showing tetrameric rings with bond lengths [pm] and angles [°].

that connect tetrameric rings into columns running along the *c* axis. Neighboring columns are alternately shifted, as shown in Figure 2.

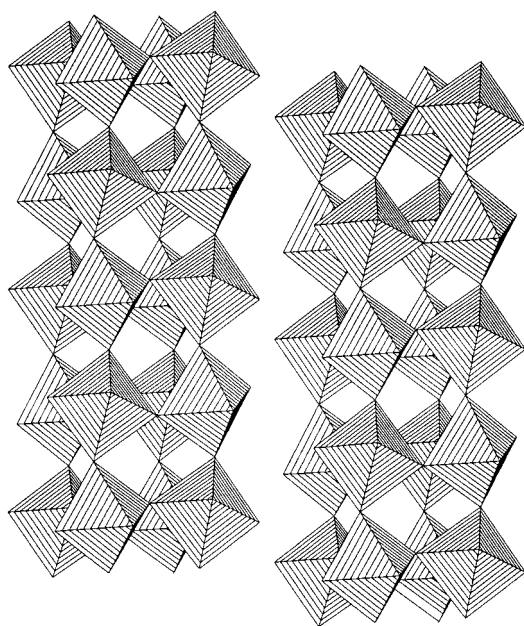


Figure 2. View perpendicularly on the shifted columns running along *c* axis in β -CrF₄.

The terminal Cr–F bond lengths are considerably shorter (168.9 to 169.6 pm) than those between Cr and bridging fluorine atoms (189.3–193.2 pm) and are comparable to corresponding bond lengths in α -CrF₄ (Cr–F_{term} 167.7, Cr–F_{br} = 187–193 pm).^[5] Angles in CrF₆ units are in the range of quite regular octahedra. The angles of the fluorine bridges Cr1–F–Cr2 that form the tetrameric rings (Figure 1) are 140.59(8) and 151.08(8)°, while Cr1–F–Cr1 and Cr2–F–Cr2 angles in columns (Figure 1) are 139.34(11), 142.86(8), and 148.12(11)°. The shortest nonbonding distances between terminal fluorine atoms and chromium atoms in neighboring columns are in the range of 355.8–392.6 pm. The shortest distances between *cis* bridging fluorine atoms (249.8–250.7 pm) are, as expected, longer than corresponding distances in the structure of α -CrF₄ (228.3 pm), which is dominated by isolated columns of edge-sharing octahedra.^[3]

Finally, there are some common structural features of all known 3d transition metal tetrafluorides. α -CrF₄ is dominated by isolated columns of edge-sharing CrF₆ octahedra.^[3] TiF₄ consists of rings formed by three corner-sharing TiF₆ octahedra,^[14] and β -CrF₄ of rings formed by four corner-sharing CrF₆ octahedra, additionally connected through *trans*-fluorine atoms into isolated infinite columns. On the other hand, tetrameric rings in VF₄ and α -MnF₄, both composed of MF₆ octahedra linked through *cis*-fluorine atoms, form layers (VF₄)^[10] or a three-dimensional network (α -MnF₄).^[15] However, the question why each of these simple 3d tetrafluorides crystalizes in a different structural type is still open.

Experimental Section

CrF₅ was prepared according to ref. [17] Single crystals of CrF₄ were prepared by slow thermal decomposition of CrF₅. At 77 K 2.3 g of CrF₅ was

sublimed into a nickel reaction vessel in an all-Teflon vacuum line equipped with Teflon valves. The autoclave was placed in an oven preheated to 403 K and kept for 5 months at this temperature. Then the reaction vessel was cooled to room temperature, and volatile components were pumped off. Some CrF₅ was still present in reaction vessel. The autoclave was opened in a dry-box under an inert atmosphere, and dark red-violet single crystals of CrF₄ were found inside. Some of them were ground for chemical analysis (calcd (%) for CrF₄: Cr 40.66, F 59.34; found: Cr 40.3, F 58.7, corresponding to molar ratio Cr:F of 1:3.99). The X-ray powder diffraction pattern of the powder obtained by grinding single crystals of CrF₄ was the same as that calculated from the crystal structure of β -CrF₄.

Crystal data:^[20] CrF₄, *M*_r = 127.99, space group *C*2/*c* (No. 15), crystal system monoclinic, *a* = 1457.0(9), *b* = 972.0(6), *c* = 719.0(4) pm, β = 102.68(2)°, *V* = 0.993(1) nm³, *Z* = 16, ρ_{calcd} = 3.42 g cm⁻³. Data collection: Mercury CCD area detector coupled with a Rigaku AFC7S diffractometer with graphite-monochromatized MoK α radiation, ω -scan technique, *T* = 200 K, θ range 2.54–30.10° in $-19 \leq h \leq 15$, $-12 \leq k \leq 13$, $-7 \leq l \leq 9$, reflections collected: 3452, independent reflections: 1211 (*R*_{int} = 0.024), observed reflections [*I* > 2 σ (*I*)]: 988, μ = 4.487 mm⁻¹, multiscan absorption correction, transmission factors: 0.280 to 0.410. The structure was solved by heavy-atom Patterson methods and expanded by using Fourier techniques. Refinement by full-matrix least-squares methods on *F*². Data-to-parameter ratio: 13.2:1. Final *R* indices: *R*1 = 0.022 [*I* > 2 σ (*I*)], *wR*2 = 0.067 [*I* > 2 σ (*I*)], *R*1 = 0.037 (all data), *wR*2 = 0.072 (all data), GOF on *F*² 1.17, largest difference peak/hole: 468/–635 e nm⁻³. Data were collected and processed with the CrystalClear (Rigaku) software suite^[18] and refined with SHELX97.^[19]

Received: August 8, 2001

Revised: January 14, 2002 [Z17691]

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Sequential Base-Promoted Annulation/ Palladium-Catalyzed Domino 1,5-Enyne Arylation and Vinylation of α - Propargylaminohydrazone

Elisabetta Rossi,* Antonio Arcadi,* Giorgio Abbiati,
Orazio A. Attanasi, and Lucia De Crescentini

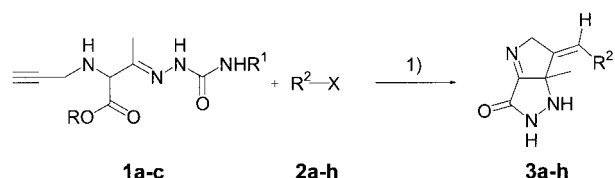
1,2-Diazabuta-1,3-dienes represent versatile building blocks in organic synthesis because they offer easy access to a wide variety of heterocyclic compounds by 1,4-conjugate addition and subsequent cyclization reactions.^[1] Moreover, Michael reaction adducts of the 1,2-diazabuta-1,3-diene system may act as nitrogen ligands^[2] for transition metal catalysts, which leads to unusual reaction pathways.^[3] In common with other Michael additions, 1,2-diazabuta-1,3-dienes undergo divergent copper-promoted annulation reactions to form functionalized imidazolines/imidazoles under regiocontrol, whereas the base-promoted cyclization provides both 1-substituted and 1-unsubstituted 4-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones.^[4]

A variety of metal-catalyzed reactions of enynes, which involve a broad range of early and late transition metals, are of interest in the synthesis of functionalized carbo/heterocycles.^[5] The classes of reaction that involve the metal-catalyzed functionalization of enynes include cycloisomerization,^[6] reductive cyclization,^[7] bismetallative cyclization,^[8] carbonylative cyclizations,^[9] and dimerization/cyclization.^[10] One-pot domino reactions of enynes provide a valuable procedure for easy access to five- and six-membered heterocycles containing a 1,3-diene structure, which can lead to bicyclic compounds through in situ Diels–Alder reactions.^[11] Domino reactions are emerging as powerful strategies in modern synthetic organic chemistry, and the discovery of new reaction sequences able to produce functional compounds constitutes a challenge both from the academic and industrial points of view.^[12]

The α -propargylaminohydrazone adducts **1a–c** (Scheme 1, Table 1), which contain a 1,4-diazo-1,6-azenyne system, turned out to be useful substrates for further metal-catalyzed processes. In this context, we investigated the palladium-catalyzed arylation and vinylation reactions of α -propargyl-

aminohydrazone. Here we report a new, efficient synthetic methodology for the preparation of (*Z*)-6-arylidene/vinylidene-6a-methyl-1,5,6a-tetrahydro-2*H*-pyrrolo[3,2-*c*]pyrazol-3-ones (for example, **3a–h**) through remarkable sequential base-promoted annulation/palladium-catalyzed, domino 1,5-ene arylation and vinylation reactions.

The treatment of **1a–c** with anhydrous piperidine in the presence of aryl iodide/triflate derivatives **2a–h** and Pd(OAc)₂/DPPF (Ac = acetyl; DPPF = 1,1'-bis(diphenylphosphanyl)ferrocene) catalytic system gave **3a–h** in good yields (Scheme 1, Table 1). The structure of compounds **3** was confirmed by one- (¹H, ¹³C) and two-dimensional (COSY, HETCOR, NOESY) NMR spectral analysis, and by mass spectroscopy. NOESY experiments clearly demonstrate that the geometry of the exocyclic double bond is *Z* for all compounds **3a–h**. Moreover, ¹H and ¹³C NMR signals arising from the vinyl substituted pyrazolones **3e–h** are split because of the presence of multiple isomers.



Scheme 1. Reagents and conditions: 1) Pd(OAc)₂, DPPF, piperidine, RT, 24 h. Spectroscopic data of new compounds can be found in the Supporting Information.

The absence of nuclear Overhauser enhancement (NOE) interactions between the olefinic protons on the exocyclic double bond and on the cyclohexene ring in **3e** was explained by the results of a conformational search^[13] at the AM1^[14] semiempirical level to evaluate the conformational energies of **3e**. The results show that the conformers with lower steric energies have spatial arrangements which are in agreement with the observed NOE interactions. Moreover, the analysis of all the observed minima show that there is only one local minimum, with a spatial arrangement compatible with a NOE interaction between the two olefinic protons (<3 Å apart), however the steric energy of this minimum is about 10 kJ mol^{−1} higher than that of the global minimum structure.

A reasonable rationale for the production of **3** is depicted in Scheme 2. The reaction involves the formation of the 1-aminocarbonyl-1*H*-pyrazol-5(2*H*)-ones **4** derivatives obtained by the piperidine-promoted annulation reaction of **1a–c**, according to our previous findings.^[4b] Solvolytic cleavage at N-1 of **4** gives **5**; ureas **6** were isolated as reaction side products. Compounds **3a–h** are formed through the palladium-catalyzed domino arylation or vinylation/carbocyclization of **5**. Thus, the regioselective *syn* addition of the σ -vinyl/aryl palladium complex on the triple bond of **7** affords the σ -vinyl palladium intermediate **8**, which forms intermediate **9** by a carbocyclopalladation step. Finally, the elimination of HPdX from **9** produces the *Z* pyrazolone derivatives **3** stereospecifically and regenerates the active catalyst. The stereochemical outcome of the reaction is in agreement with the sequence illustrated in Scheme 2 and with the results

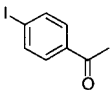
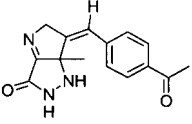
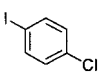
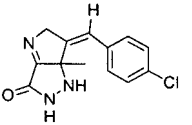
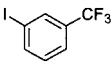
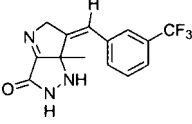
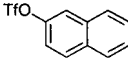
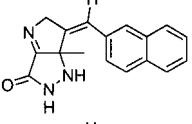
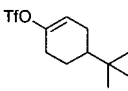
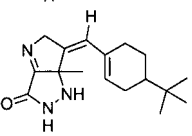
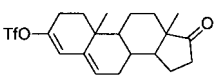
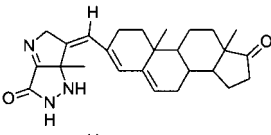
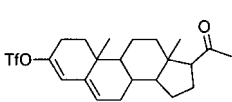
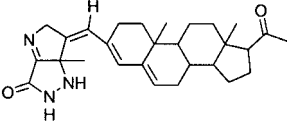
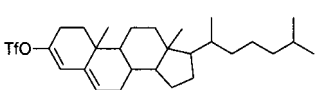
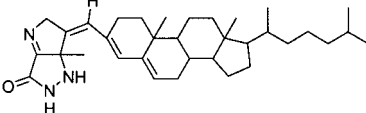
[*] Dr. E. Rossi, Dr. G. Abbiati
Istituto di Chimica Organica, Facoltà di Farmacia
Università di Milano
Via Venezian 21, 20133 Milano (Italy)
Fax: (+39) 02-5835-4476
E-mail: Elisabetta.Rossi@unimi.it

Prof. A. Arcadi
Dipartimento di Chimica Ingegneria Chimica e Materiali, Facoltà di Scienze, Università di L'Aquila
Via Vetoio, Coppito Due, 67100 L'Aquila (Italy)
Fax: (+39) 08-6243-3756
E-mail: Arcadi@univaq.it

Prof. O. A. Attanasi, Dr. L. De Crescentini
Istituto di Chimica Organica, Università di Urbino
Piazza della Repubblica 13, 61029 Urbino (Italy)

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

Table 1. Compounds **1**–**3**.

1	R	R ¹	2	Structure	3	Structure	Yield ^[a] [%]
a	Me	H	a		a		67
b	Et	H	b		b		68
c	Me	Ph	c		c		67
			d		d		64
			e		e		62
			f		f		66
			g		g		64
			h		h		65

[a] Yields refer to single runs and isolated products.

obtained in the bimetallic palladium-catalyzed cyclization of enynes.^[8]

Although the Pd^{II}-catalyzed intramolecular cyclization of enynes has been utilized for the preparation of five-membered ring systems,^[6a, 15] to our knowledge, the sequential palladium-catalyzed reaction reported here is the first example of a domino, palladium-catalyzed, intermolecular arylation/vinylation combined with an intramolecular^[16] carbopalladation process of a 1,5-enyne derivative, which leads to fused heterocycles through a regioselective 5-*endo-dig* annulation reaction, followed by β -hydride elimination with cleavage of the N–H bond. Only a few examples of σ -aryl/vinyl palladium complexes involved in cascade^[17] carbopalladation and domino palladium-catalyzed intermolecular arylation/vinylation-intramolecular^[14] carbopalladation processes of 1,6- or 1,7-enynes have been reported.

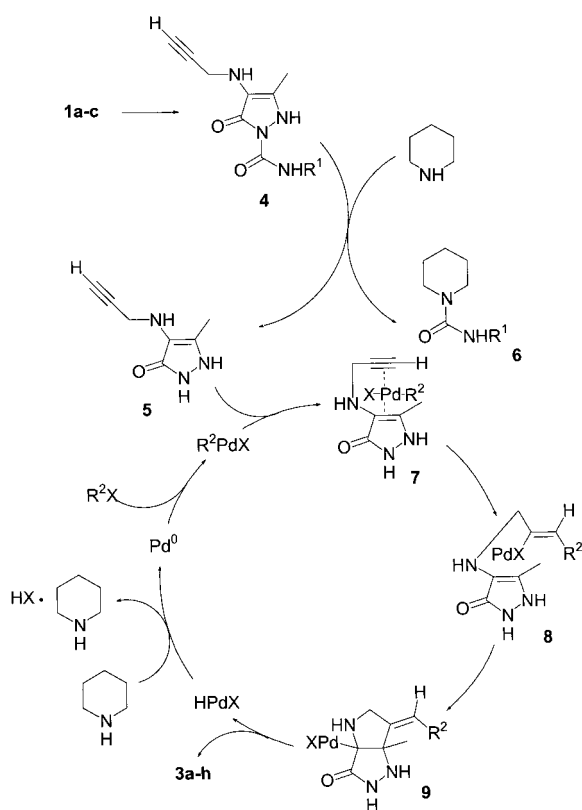
In conclusion, we have developed a new efficient Pd-catalyzed ene-type carbocyclization and current efforts are now focused on these and related substrates, to access the synthetic potential of this procedure.

Experimental Section

The appropriate halides or triflates **2a–h** (1 mmol), Pd(OAc)₂ (11.22 mg, 0.05 mmol), and DPPF (27.72 mg, 0.05 mmol) were added to a nitrogen-flushed solution of **1a–c** (1 mmol) in dry piperidine (6 mL). The reaction mixture was stirred at room temperature for 24 h, poured into HCl (0.1 M, 100 mL) and extracted twice with ethyl acetate. The organic layer was dried over Na₂SO₄, evaporated to dryness, and the crude product was purified by flash chromatography on silica gel. Elution with petroleum ether/ethyl acetate afforded pure **3a–h**.

3a: M.p. 139.7–141.9 °C; IR (KBr): $\tilde{\nu}$ = 3360, 3186, 1718, 1682, 1560 cm^{−1}; ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 1.98 (s, 3H, CH₃), 2.58 (s, 3H, CH₃CO), 2.93 (br s, 1H, D₂O-exchange, NH), 4.05 (dd, ³J(H,H) = 15 Hz, ⁴J(H,H) = 2 Hz, 1H, CH₂), 4.35 (dd, ²J(H,H) = 15 Hz, ⁴J(H,H) = 2 Hz, 1H, CH₂), 6.70 (t, ⁴J(H,H) = 2 Hz, 1H, =CH), 7.32 (d, ³J(H,H) = 7.8 Hz, 2H, aromatic), 7.88 (d, ³J(H,H) = 7.8 Hz, 2H, aromatic), 8.82 (br s, 1H, D₂O-exchange, NH); ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 13.9 (CH₃), 26.9 (CH₃CO), 54.9 (CH₂), 78.2 (C_{sp3}), 126.2 (C_{sp2}H, 2C; aromatic), 129.3 (C_{sp2}H, 2C; aromatic), 134.6 (=C_{sp2}H), 137.0 (C_{sp2}), 137.2, (C_{sp2}), 138.0, (C_{sp2}), 164.1 (C=N), 178.1 (C=O), 197.8 (C=O); MS (70 eV): *m/z* (%): 269 (100) [*M*⁺]; Elemental analysis calcd (%) for C₁₇H₁₅N₃O: C 73.62, H 5.45, N 15.15; found: C 73.79, H 5.57, N 14.85.

Received: November 29, 2001 [Z18300]



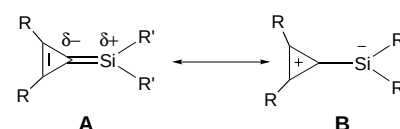
Scheme 2. A plausible catalytic cycle for the formation of **3**.

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The First Isolable 4-Silatriafulvene**

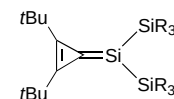
Kenkichi Sakamoto,* Jun Ogasawara, Yoshihiro Kon, Tatsuya Sunagawa, Chizuko Kabuto, and Mitsuo Kira*

Among various silicon–carbon doubly bonded compounds (silaethenes),^[1] 4-silatriafulvenes have attracted much attention because of their unique electronic properties;^[2, 3] the intrinsic polarity of the Si=C bond in 4-silatriafulvene (**A**) is expected to be reduced by the significant contribution of resonance structure **B** (Scheme 1).



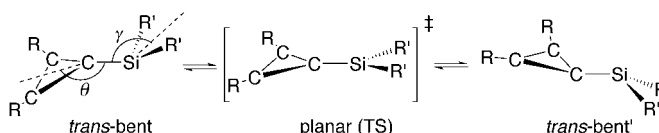
Scheme 1.

We recently generated the first 4-silatriafulvene derivative, 1,2-di-*tert*-butyl-4,4-bis(trimethylsilyl)-4-silatriafulvene (**1a**),^[2] as a reactive intermediate and demonstrated that **1a** is much less reactive toward *tert*-butyl alcohol than is usual for silaethenes and isomerizes to the corresponding silacyclobutadiene at high temperatures. Theoretical calculations for 4-silatriafulvene derivatives have predicted the fluxional nature of the 4-silatriafulvene skeletons, which are not planar around the Si=C bond but *trans*-bent, with large bend angles and an energy difference of only 1.0 kcal mol⁻¹ between the *trans*-bent and planar structures at the MP2/6-311++G**+ZPE level (Scheme 2).^[3d]



1a, SiR₃ = SiMe₃

1b, SiR₃ = SiMe₂tBu



Scheme 2. Skeletal inversion of silatriafulvene.

Although Schumann et al. have reported the isolation of stable 4-germa-, 4-stanna-, and 4-plumbatriafulvenes,^[4] no stable 4-silatriafulvene has been synthesized to date.^[5] By use of bulky *tert*-butyldimethylsilyl groups instead of trimethylsilyl groups in **1a**, we synthesized the first stable 4-silatria-

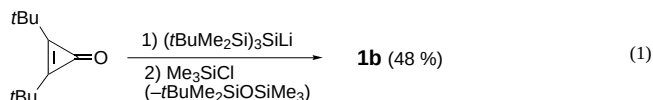
[*] Prof. K. Sakamoto,^[†] Dr. J. Ogasawara, Y. Kon, T. Sunagawa, Dr. C. Kabuto, Prof. M. Kira
Department of Chemistry,
Graduate School of Science
Tohoku University, Aoba-ku, Sendai 980-8578 (Japan)
Fax (+81) 22-217-6589
E-mail: mkira@si.chem.tohoku.ac.jp

[*] Concurrent office:
Photodynamics Research Center
The Institute of Physical and Chemical Research (RIKEN)
519-1399 Aoba, Aramaki, Aoba-ku, Sendai 980-0845 (Japan)

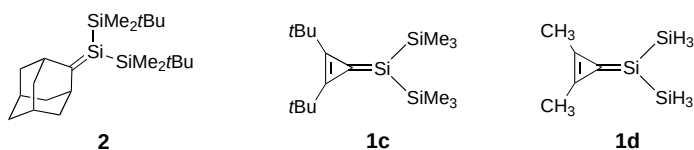
[**] This work was supported by the Japanese Ministry of Education, Culture, Sports, Science, and Technology [Grant-in-Aid for Scientific Research (B) No. 11440185].

fulvene, 1,2-di-*tert*-butyl-4,4-bis(*tert*-butyldimethylsilyl)-4-silatriafulvene (**1b**), and revealed its structural characteristics by NMR and UV spectroscopic studies and X-ray crystallography. The addition of methanol to **1b** occurred with unusual regioselectivity compared with the corresponding reactions of common silaethenes.

The sila-Peterson reaction^[6, 7] of di-*tert*-butylcyclopropenone with tris(*tert*-butyldimethylsilyl)silyllithium successfully gave the corresponding silatriafulvene **1b** as yellow crystals (48 % yield) [Eq. (1)].^[8] Although **1b** was extremely sensitive to air and moisture, neither decomposition nor dimerization took place for several months at room temperature in an inert atmosphere.



In good accord with the unique electronic structure of 4-silatriafulvene, in the NMR spectrum, the resonance signal of the unsaturated ²⁹Si nucleus in **1b** in [D₆]benzene appeared at an extraordinarily high field $\delta_{\text{Si}} = -71.9$, which is 122 ppm higher than that of bis(*tert*-butyldimethylsilyl)adamantylidenesilane (**2**; Scheme 3; $\delta_{\text{Si}} = +50$)^[6b]. The position of the



Scheme 3.

observed ²⁹Si resonance signal is in good agreement with that of the unsaturated silicon atom in a model silatriafulvene **1c** ($\delta_{\text{Si}} = -68.7$) calculated at the bent equilibrium structure, by using the GIAO method at the HF/6-31G*/MP2/6-31G* level. The remarkable upfield shift is the result of the less polar nature of the Si=C bond caused by the significant contribution of resonance structure **B** (Scheme 1) in **1b**, compared with **2** and other common silaethenes.^[9]

The molecular structure of **1b**, determined by X-ray crystallography, was not consistent with the predicted bent form.^[12] As shown in Figure 1, **1b** in the solid state has an almost planar skeleton with bond alternation; all the skeletal carbon and silicon atoms are located almost in a plane with bend angles θ and γ of 166.1° and 170.9°, respectively,^[13] and the unsaturated silicon-carbon bond length is 1.755 Å, which is close to that of *tert*-butyldimethylsilyl(trimethylsilyl)-adamantylidenesilane (1.741 Å).^[6b] The X-ray structure of **1b** does not resemble the optimized bent structure but the planar transition structure of the model silatriafulvene **1c** (Scheme 3). The discrepancy between the X-ray structure and the theoretical equilibrium structure is explained by the packing force in the crystal, which is larger than the very small energy required for the deformation of the bent structure to the planar structure.

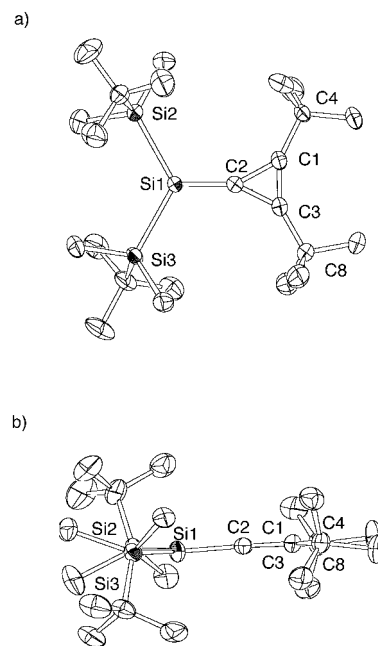
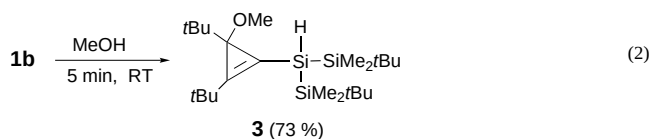


Figure 1. ORTEP drawings of **1b**. a) Top view, b) side view. Hydrogen atoms are omitted for clarity. The thermal ellipsoids are set at the 50 % level. Selected bond lengths [Å] and bond angles [°]: Si1-Si2, 2.3335(8); Si1-Si3 2.3420(7), Si1-C2 1.755(2), C1-C2 1.450(3), C1-C3 1.309(3), C1-C4 1.496(3), C2-C3 1.447(3), C3-C8 1.497(3); Si2-Si1-Si3 120.21(3), Si2-Si1-C2 119.65(7), Si3-Si1-C2 119.71(7), C2-C1-C3 63.1(1), C2-C1-C4 144.6(2), C3-C1-C4 152.2(2), Si1-C2-C1 152.0(2), Si1-C2-C3 154.1(2), C1-C2-C3 53.7(1), C1-C3-C2 63.2(1), C1-C3-C8 150.6(2), C2-C3-C8 146.1(2).

The fluxional character of 4-silatriafulvene (Scheme 2) was, as predicted by theoretical calculations, evidenced by the significant temperature dependence in the ²⁹Si NMR and UV spectra of **1b**. The $\delta_{\text{Si}} = -73.7$ signal of **1b** at 298 K shifted to $\delta_{\text{Si}} = -77.0$ at 190 K in [D₈]THF, and the UV absorption maximum (λ_{max}) that appeared at 352 nm ($\epsilon = 16000$) in 3-methylpentane at 298 K was blue-shifted and its intensity increased by lowering the temperature; λ_{max} reached 344 nm with $\epsilon = 33000$ at 77 K. The GIAO calculations for the planar and bent structures of **1c** have shown that the δ_{Si} values are -68.7 and -61.2 , respectively, at the HF/6-31G*/MP2/6-31G* level.^[3g] CIS calculations have revealed that the $\pi-\pi^*$ transition band for the planar structure of **1d** should appear at 310 nm with an oscillator strength f of 0.065, while that for the bent structure should appear at 303 nm with an f of 0.346.^[3g] The temperature dependence observed in the ²⁹Si NMR and UV spectra of **1b** is consistent with the idea that, at high temperature, the structure of **1b** fluctuates around the planar structure with large bending amplitudes, but at low temperature, **1b** freezes to the bent equilibrium structure.

While silatriafulvene **1b** did not react appreciably with *tert*-butyl alcohol over a couple of days at room temperature,^[14] **1b** reacts with methanol instantaneously at room temperature to give **3** in 73 % yield [Eq. (2)].^[15] Interestingly, the regioselectivity



tivity was completely opposite to that for the alcohol addition to common silaethenes, which indicates the significant contribution of the resonance form **B** in **1b** (Scheme 1); the OH hydrogen and methoxy groups of methanol were bonded to the unsaturated silicon atom and a ring carbon atom in **1b**, respectively.^[16]

Received: December 14, 2001 [Z18381]

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- [8] **1b**: Yellow crystals; m.p. 95 °C (decomp.); ¹H NMR (300 MHz, [D₆]benzene, TMS): δ = 0.47 (s, 12H), 1.16 (s, 18H), 1.17 (s, 18H); ¹³C NMR (75 MHz, [D₆]benzene, TMS): δ = 0.2, 19.6, 28.5, 28.6, 32.9, 157.0 (C=C), 159.9 (Si=C, ¹J_{SiC} = 66 Hz); ²⁹Si NMR (59 MHz, [D₆]benzene, TMS): δ = –71.9 (Si=C, ¹J_{SiC} = 66 Hz), 1.7 (SiBuMe₂); HRMS calcd for C₂₃H₄₈Si₃ 408.3064 found 408.3060.
- [9] Typical δ_{Si} values for (Me₃SiO)(Ad)C=Si(SiMe₃)₂ (Ad = adamantyl) and (Me₃Si)(tBuMe₂Si)C=SiMe₂ are +42 and +144, respectively.^[10] Recently, negative δ_{Si} values for the unsaturated silicon nuclei have been found in 1-aza-3-silaallene (δ_{Si} = –57)^[11] and hexaphenylsilalene (δ_{Si} = –28)^[5] with rather less polar Si=C double bonds.
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- [12] Recrystallization of **1b** from heptane gave single crystals suitable for X-ray structural analysis. X-ray analysis of **1b**: M_F = C₂₃H₄₈Si₃, M_W = 408.89, monoclinic, space group P2₁/c, a = 11.0141(8), b = 17.9026(9), c = 14.210(3) Å, β = 91.173(2)°, V = 2801.4(7) Å³, Z = 4, ρ_{calcd} = 0.969 g cm^{–3}, μ(MoKα) = 1.75 cm^{–1}. The reflection intensities were collected on a Rigaku/MSC Mercury CCD diffractometer (50 kV,

40 mA) with graphite monochromated MoKα radiation (λ = 0.71069 Å) at 150 K. The structure was solved by direct methods, by using SIR-92, and refined by full-matrix least-squares analysis on F. A total of 6392 reflections were measured, and of these, 4509 reflections [F_o > 3.00σ(F_o)] were used in refinement: R = 0.041, R_w = 0.044. CCDC-175782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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).

- [13] The bend angles θ and γ are defined as the angles between the three-membered-ring plane and the Si(unsaturated)–C bond, and between the R₂Si plane and the Si(unsaturated)–C bond, respectively (Scheme 2). Theoretical bend angles θ and γ for **1c** in the bent structure are 171.8 and 141.5°, respectively.^[3g]
- [14] The reaction of **1b** with *tert*-butyl alcohol in hexane under reflux afforded the alcohol adducts of the corresponding silacyclobutadiene as expected.^[2] Details will be reported elsewhere.
- [15] **3**: a colorless oil; ¹H NMR (300 MHz, C₆D₆): δ = 0.21 (s, 3H), 0.25 (s × 2, 6H), 0.27 (s, 3H), 1.00 (s × 2, 18H), 1.18 (s, 9H), 1.22 (s, 9H), 3.02 (s, 3H), 4.24 (s, 1H); ¹³C NMR (75 MHz, C₆D₆): δ = –2.92, –2.87, –2.60, –2.41, 18.51, 18.59, 27.65, 29.41, 30.51, 32.73, 38.09, 53.95, 76.42, 115.25, 156.53; ²⁹Si NMR (59 MHz, C₆D₆): δ = –90.24 (d, ¹J(Si,H) = 155 Hz), –1.92, –1.43; MS (70 eV) m/z (%) 425 (M⁺ – 15, 6), 259 (6), 147 (100), 115 (6).
- [16] Similar inverted regioselectivity has been observed for a silacalene by West et al.^[5]

Aldolase-Catalyzed Asymmetric Synthesis of Novel Pyranose Synthons as a New Entry to Heterocycles and Epothilones**

Junjie Liu and Chi-Huey Wong*

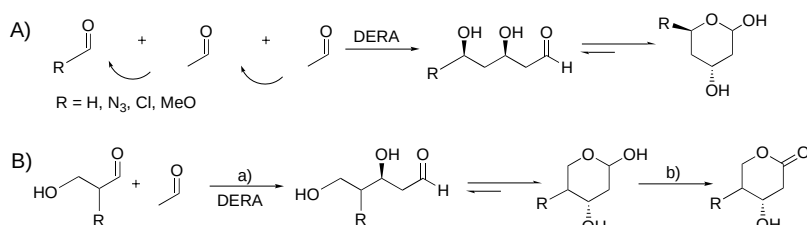
The enzyme 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4), a Schiff base forming type I class aldolase, catalyzes the reversible aldol reaction of acetaldehyde and D-glyceraldehyde 3-phosphate (G3P) to form D-2-deoxyribose-5-phosphate (DRP).^[1] The enzyme has been overexpressed in *Escherichia coli*, and its structure and catalytic mechanism have been determined at the atomic level.^[2]

DERA accepts a broad range of acceptor and donor aldehydes in addition to the natural substrates.^[1] An interesting transformation is the sequential asymmetric aldol addition reaction of three achiral aldehydes to form pyranoses with two new stereogenic centers (Scheme 1 A).^[3] In this sequential reaction, the first aldol product acts as a substrate for the second aldol reaction to give an enantiomerically pure 3,5-

[*] Prof. Dr. C.-H. Wong, J. Liu
Department of Chemistry and the Skaggs Institute for Chemical Biology
The Scripps Research Institute, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2409
E-mail: wong@scripps.edu

[**] This work was supported by the NIH GH44154. We thank Dr. G.-J. Shen for the preparation of 2-deoxyribose-5-phosphate aldolase (DERA) and Dr. D.-H. Huang and Dr. L. B. Pasternack for NMR assistance.

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



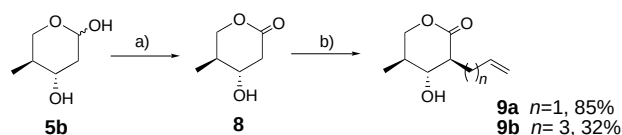
Scheme 1. Preparation of unnatural pyranoses with DERA. a) pH 7.5, DERA, acetaldehyde; b) Br_2 , $BaCO_3$. For details of routes A and B see text.

dihydroxyaldehyde which then cyclizes to form the stable pyranose, thus driving the reaction toward condensation. Since these 1,3-polyol systems are useful synthons,^[4] we have further examined the scope of this enzymatic methodology. Our strategy is to exploit β -hydroxyaldehydes as acceptors (Scheme 1B) to generate the products which would cyclize to form stable hemiacetals, thus driving the reaction toward condensation. The hemiacetal could be further oxidized to give a lactone. We have found that the oxidation sometimes makes the purification much easier, and more importantly, the lactone can be further transformed to other useful synthons. Several different substrates have been tested and the results are summarized in Table 1.

The configuration of C2 in the acceptor aldehydes is very critical for the enzymatic reaction. We found that D isomers were overwhelmingly preferred over L isomers when polar groups (e.g. OH, N_3) were at this position; when racemic acceptor aldehydes were used, only the D isomer products were formed (Table 1, entries 2–4). On the contrary, an opposite enantioselectivity was observed when a hydrophobic

group is at the C2 position (Table 1, entries 5–7): **5a** afforded lactone **5b** in 48% yield after two steps, while its enantiomer **6a** only gave **6b** in trace amounts, and racemic aldehyde **7a** only produced **7b**. Molecular modeling based on the structure of DERA^[2] reveals a hydrophilic binding pocket composed of Thr170 and Lys172 for the OH group at C2 and a hydrophobic pocket for the H atom at C2. A switch of the binding was observed for **5a** and **7a** in which the methyl and the methoxy groups are in the hydrophobic pocket, which results in the change of enantioselectivity.

The 1,3-polyol systems prepared from the enzymatic reaction could serve as useful synthons.^[5–8] An example is the stereoselective C2 alkylation of β -hydroxylactone with an alkyl bromide under chelation control directed by the β -hydroxy group (Scheme 2).^[9] This reaction can provide more diversified pyranoses after reduction of the lactones^[10] and generate additional useful intermediates for organic synthesis. In our alkylation experiment, the other diastereomers were not detected. The relative configuration of **9a** was unequivocally confirmed by NMR experiments.



Scheme 2. Stereoselective alkylation. a) Br_2 , $BaCO_3$, 12 h, 62%; b) LDA, HMPA, $-78^\circ C$, alkyl bromide, 36 h. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide.

Table 1. Aldol condensation catalyzed by DERA.

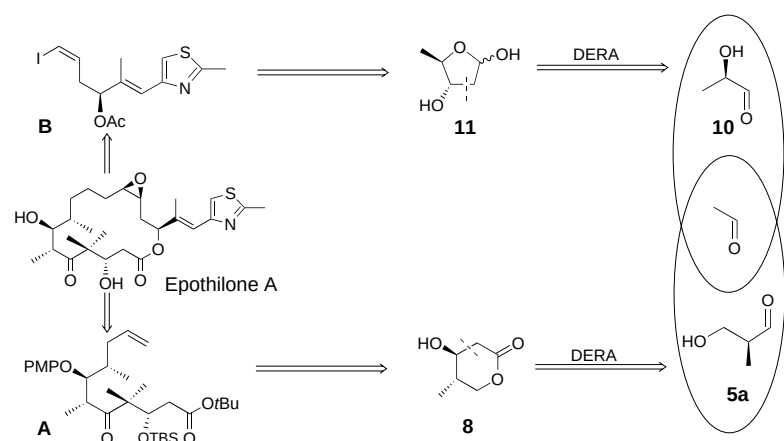
Entry	Acceptor	Donor	t [days]	Product	Yield [%]
1			3		65
2			3		60 ^[a]
3			3		47 ^[a]
4			6		28 ^[a]
5			3		48 ^[b]
6			6		trace ^[b]
7			6		22 ^[a]

[a] Based on the reactive enantiomers. [b] Total yield for two steps from protected aldehyde.

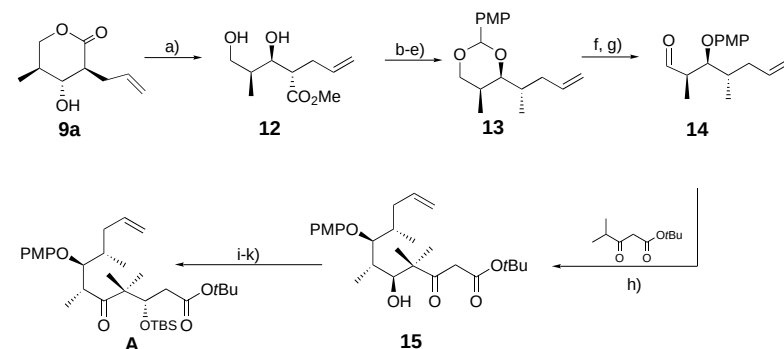
The availability of both intermediates **9a** and **9b** permitted us to choose either the Suzuki coupling^[11a,b,k-n] or olefin metathesis strategy^[11c-h,p,q] to prepare epothilones as potential anticancer agents.^[12] Since allyl bromide is more active and gives **9a** in a higher yield, the Suzuki coupling strategy was chosen for the construction of the C12–C13 Z double bond (Scheme 3). In addition to **9a**, compound **11** prepared by DERA was also used as a key synthon.^[13]

In our synthesis of fragment **A** (Scheme 4), the lactone ring of **9a** was first opened to afford diol **12**, which was then protected as the PMP acetal. After reduction by $LiAlH_4$, the hydroxy was removed by mesylation followed by reduction, both in excellent yield.^[14] Regioselective cleavage of the PMP protecting group in **13** with DIBAL in toluene gave the primary alcohol as the only product, which was oxidized with Dess–Martin periodinane^[15] to give aldehyde **14**. Compound **14** was then condensed with *tert*-butyl isobutyrylacetate^[11b, 16] to give compound **15** in 70% yield (d.r. 8:1). Stereoselective reduction with $Me_4NBH(AcO)_3$ ^[17] resulted in the formation of the desired diol (d.r. 10:1). Regioselective silylation of the β -hydroxy group followed by oxidation gave fragment **A**.

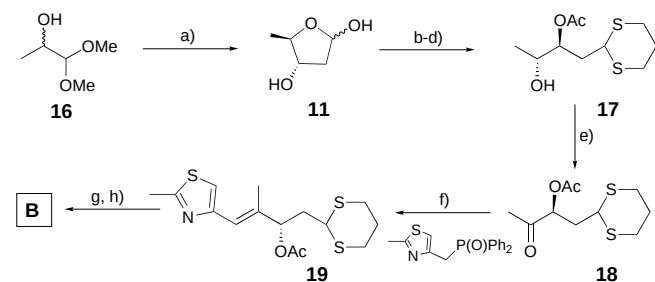
Because the configuration of C2 in **16** is not essential in our synthetic route (Scheme 5), racemic lactaldehyde acetal **16** was used in our current synthesis. Interestingly, we found that only the D isomer was accepted as a substrate for DERA and no L isomer product was detected in our experiment.



Scheme 3. Retrosynthesis of epothilone A and C. PMP = 4-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.



Scheme 4. Synthesis of fragment A. a) MeONa, -30°C , 60%; b) anisaldehyde dimethyl acetal, CSA, 95%; c) LiAlH_4 , 0°C –RT, 90%; d) MsCl, NEt_3 , 94%; e) LiAlH_4 , 88%; f) DIBAL, toluene, 93%; g) Dess–Martin oxidation, 96%; h) NaH, *n*BuLi, 0°C , 70%; i) $\text{Me}_4\text{NBH}(\text{OAc})_3$, -30°C , 83%; j) TBSOTf, 2,6-lutidine, 0°C , 10 min, 100%; k) Dess–Martin oxidation, 3 h, 90%. CSA = 10-camphorsulfonic acid, PMP = 4-methoxyphenyl, Ms = mesyl = methanesulfonyl, DIBAL = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl.



Scheme 5. Synthesis of fragment B. a) Dowex(H^+), 40°C , then pH 7.5, DERA, acetaldehyde, three days, 38% (two steps based on the D enantiomer); b) AcCl, pyr, 95%; c) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{H}_2\text{O}/\text{CH}_3\text{CN}$, 0°C , 84%; d) 1,3-propanedithiol, TiCl_4 , -78°C , 97%; e) DMSO, $(\text{COCl})_2$, 95%; f) *n*BuLi, THF, -78°C , 88%; g) $\text{Hg}(\text{ClO}_4)_2$, CaCO_3 , THF/ H_2O , RT, 2 h; h) $\text{Ph}_3\text{P}=\text{CHI}$, $\text{NaN}(\text{TMS})_2$, HMPA, THF, -78°C , 60% (two steps). Ac = acetyl, pyr = pyridine, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, TMS = trimethylsilyl.

The preparation of fragment B is rather straightforward (Scheme 5). The β -hydroxy group of **11** was selectively protected and the hemiacetal was treated with 1,3-propanedithiol to afford the dithiane **17**, which was oxidized to ketone **18** in 95% yield. Wittig reaction of **18** with a phosphine oxide

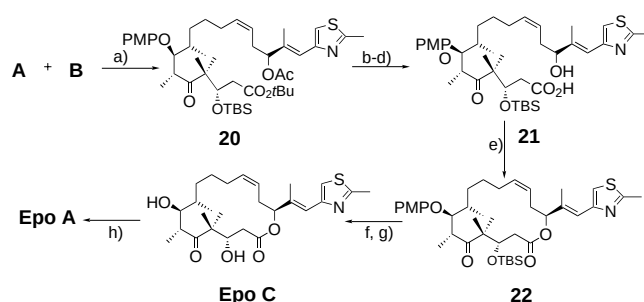
afforded **19**.^[11b, 18] Following deprotection of the dithiane with $\text{Hg}(\text{OCl}_4)_2$,^[19] the aldehyde product was directly coupled with $(\text{Ph}_3\text{P}^+\text{CH}_2\text{I})^-$ ^[20] to afford fragment B in 60% yield for the two steps.

The Suzuki coupling of fragments A and B proceeded smoothly as described by Danishefsky et al.^[11b] to afford **20** (Scheme 6). After the acetyl and *tert*-butyl ester protecting groups were removed, the hydroxy acid **21** was subject to Yamaguchi macrolactonization conditions^[21] to afford the intermediate **22**. The PMP and TBS protecting groups were removed with DDQ^[22] and HF·pyr, respectively, to furnish epothilone C (Epo C). Epoxidation with a freshly prepared solution of 1,3-dimethyldioxirane (DMDO)^[23] afforded synthetic epothilone A (Epo A) with physical properties ($[\alpha]_D$, ^1H , ^{13}C NMR, MS, IR) identical to the reported data.^[11g]

In summary, we have developed a new strategy for the synthesis of unnatural pyranose synthons through enzymatic reactions catalyzed by DERA. This strategy is very convergent and effective. Coupled with β -hydroxy-directed highly stereoselective alkylation, diversified 1,3-polyols can be prepared. Their application to natural product synthesis has been illustrated by the concise total synthesis of epothilones A and C.

Received: December 17, 2001 [Z18398]

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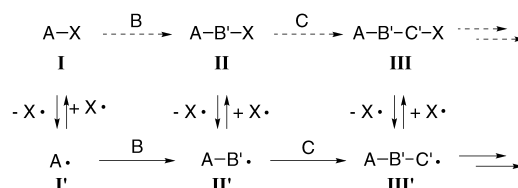
Scheme 6. Final steps for the synthesis of epothilone A. a) $[\text{PdCl}_2(\text{dppf})]$, Ph_3As , Cs_2CO_3 , 9-BBN, 65%; b) MeONa(cat.), MeOH, 85%; c) TMSOTf, 2,6-lutidine; d) NaOH(cat.) MeOH, 78% for two steps; e) Yamaguchi conditions, 85%; f) DDQ, CH_2Cl_2 , 99%; g) HF·Pyr, THF, 95%; h) DMDO, 45%. dppf = bis(diphenylphosphanyl)ferrocene, 9-BBN = 9-borabicyclo[3,3,1]nonane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMDO = 3,3-dimethyldioxirane.

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Convergent Synthesis of Silylated Allylic Alcohols by a Stereoselective Domino, Sequential Radical-Coupling Reaction**

Shigeru Yamago,* Masaki Miyoshi, Hiroshi Miyazoe, and Junichi Yoshida*

The construction of multiple carbon–carbon bonds by tandem reactions represents an efficient approach to the synthesis of complex molecular structures from simple organic building blocks.^[1] Although radical-mediated intra-molecular tandem cyclization exemplifies such an approach,^[2] extensions to the intermolecular reaction (Scheme 1; **I'**–**III'**) have been severely limited, and require careful choice of



Scheme 1. A–X: Radical precursor; B, C: radical acceptors.

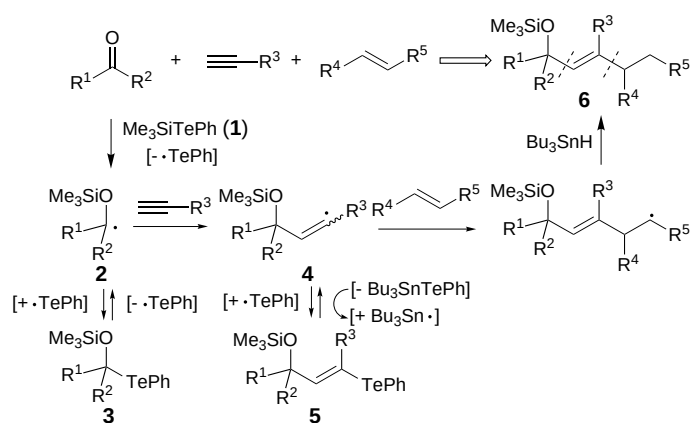
coupling partners.^[3] This limitation could be attributed to the difficulty in the selective reaction of the transient radicals, for example, **I'**, **II'**, and **III'**, with certain coupling partners in radical chain reactions. The problem might be solved if we could prepare the radical intermediates **I'**, **II'**, and **III'** as their radical precursors **I**, **II**, and **III**, and subsequently couple them with radical acceptors in an atom- or group-transfer manner (Scheme 1).^[4] The reaction would then be an iterative atom- or group-transfer radical reaction.^[5] However, there have been no reports of such transformations, with the exception of living radical polymerization, in which the same alkenes react consecutively.^[6]

We have reported the group-transfer coupling of trimethylsilyl phenyl telluride (**1**), carbonyl compounds, and isonitriles, which involves the selective carbon–carbon bond formation of the α -siloxy radical **2** with isonitriles.^[7] It should be noted that the reaction of silyl tellurides with carbonyl compounds in the absence of isonitrile afforded the α -siloxy telluride **3**. This unique feature of the reaction prompted us to investigate alkynes as a third coupling partner (Scheme 2). Here we report a novel group-transfer coupling of **1**, carbonyl compounds, and alkynes to give the silylated allylic alcohol **5**. As the product also possesses a reactive carbon–tellurium bond, radical-mediated transformation via the vinyl radical **4**

[*] Prof. S. Yamago, Prof. J. Yoshida, M. Miyoshi, Dr. H. Miyazoe
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering
Kyoto University, Kyoto 606-8501 (Japan)
Fax: (+81)75-753-5911
E-mail: yamago@sbchem.kyoto-u.ac.jp
yoshida@sbchem.kyoto-u.ac.jp

[**] This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. We thank Dr. K. Itami for the X-ray analysis.

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would effect further carbon–carbon bond formation, thus providing a convergent and stereoselective synthetic route to allylic alcohols with tri-substituted carbon–carbon double bonds.^[8]

The sequential reaction to form **5** (method A) was initially examined by using **1**, benzophenone, and phenyl acetylene as substrates. Compound **1** and benzophenone were treated at room temperature in MeCN to give **3a** ($R^1, R^2 = \text{Ph}$), which was treated with phenyl acetylene at 100 °C to give **5a** ($R^1, R^2, R^3 = \text{Ph}$) in 85 % yield.^[9] Alternatively, the reaction was accomplished in one step by heating a mixture of **1** (1.2 equivalents), benzophenone (1.0 equivalents), and phenyl acetylene (1.2 equivalents) without solvent at 100 °C for 12 h (method B) to give **5a** in 93 % yield after recrystallization. Owing to its simplicity, we routinely used method B. The reaction does not require the use of a solvent, although various solvents, such as EtCN, $(\text{CH}_2\text{Cl})_2$, and supercritical CO_2 , could be also used.

The reaction showed high *E* selectivity (96 %), which was confirmed by X-ray structural analysis.^[10] The X-ray analysis also confirmed the regioselectivity; the addition of the α -siloxy radical **2a**, which is generated from **1** and benzophenone, took place at the less hindered side of the alkyne. The subsequent group-transfer reaction of the resulting vinyl radical **4** gave rise to the formation of **5** (Scheme 2). As the stereochemistry is controlled kinetically (see below), the group-transfer takes place from the less hindered side of **4**, to avoid steric interaction with the bulky siloxyalkyl moiety.

The present reaction is applicable to a variety of carbonyl compounds and alkynes, and its scope and efficiency are summarized in Table 1. Since a variety of R^1 , R^2 , and R^3 groups can be used, the present reaction would be useful for the diversity-oriented synthesis of allylic alcohol derivatives. Aromatic ketones and aldehydes (entries 1–8 and 10) are especially good substrates. The reaction with electron-rich alkynes was completed within 4–12 h at 100 °C in most cases and gave the desired coupling product in good to excellent yields. Aliphatic ketones and aldehydes were less reactive and required longer reaction times, but the reaction eventually afforded the desired coupling products in good yields (entries 9 and 11). Aryl- and heteroaryl-substituted alkynes and conjugated enynes were excellent acceptors, and the

Table 1. Synthesis of silylated allylic alcohols **5**.^[a]

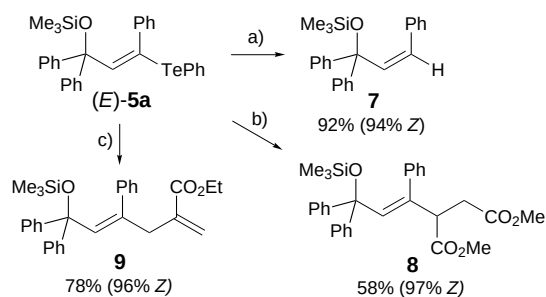
Entry	Ketone (R^1, R^2)	Alkyne (R^3)	Time [h]	Yield [%]	(<i>E</i> : <i>Z</i>) ^[b]
1	Ph, Ph	Ph	12	93	96:4
2 ^[c]	Ph, Ph	<i>p</i> -EtO ₂ C-C ₆ H ₄	12	78	93:7
3 ^[c]	Ph, Ph	<i>p</i> -Br-C ₆ H ₄	12	97	93:7
4 ^[c]	Ph, <i>p</i> -MeO-C ₆ H ₄	Ph	12	77 (93) ^[d]	95:5
5 ^[c]	Ph, <i>p</i> -Me ₂ N-C ₆ H ₄	Ph	12	61	90:10
6 ^[c]	Ph, Ph	3-pyridyl	12	82	80:20
7 ^[c]	Ph, Ph	1-cyclohexenyl	12	64 (87) ^[d]	92:8
8	Ph, <i>i</i> Pr	Ph	36	51	93:7
9	-(CH ₂) ₃ -	Ph	40	66	87:13
10	Ph, H	Ph	4	74 (82) ^[d]	74:26
11	<i>c</i> -C ₆ H ₁₁ , H	Ph	36	82	67:33
12 ^[c,e]	Ph, Ph	CO ₂ Et	2	69	85:15

[a] A mixture of **1** (1.3 equiv), carbonyl compound (1.0 equiv) and alkyne (2.0 equiv) was heated at 100 °C in a sealed tube. Full experimental details and characterization data can be found in the Supporting Information. [b] The ratio was determined by ¹H NMR of the crude reaction mixture. [c] The reaction was carried out in propionitrile or CD₃CN (about 0.6 M concentration of starting carbonyl compound). [d] Yield based on the converted carbonyl compounds. [e] The reaction was carried out in a stepwise manner.

reaction gave the desired coupling products in good to excellent yields (entries 1–3, 6 and 7; where $R^1 = R^2 = \text{Ph}$). The reaction with electron-deficient alkynes such as acetylene carboxylic esters, however, did not give the desired coupling products because of the preferential reaction of **1** with the alkynes. Method A was effective in such cases, and the coupling of **3a** with ethyl propiolate at 100 °C for 2 h afforded the desired coupling product **5b** ($R^1, R^2 = \text{Ph}, R^3 = \text{CO}_2\text{Et}$) in good yield (entry 12).

The high *E* stereoselectivity of the olefinic moiety of the products is remarkable, when it is considered that these reactions took place at 100 °C. Because the isolated (*E*)-**5b** and (*Z*)-**5b** did not show any signs of stereochemical isomerization even under the harsher reaction conditions of 100–130 °C for 13 h, the stereochemistry is controlled kinetically, although we have already reported that structurally related vinyl tellurides undergo stereochemical isomerization under photo-irradiation.^[8c] The level of selectivity is more than 9:1 in the reaction with most of the ketones used, while in the reaction with aldehydes and sterically less hindered ketones, such as cyclobutanone, the level is slightly lower. The observed decrease in selectivity is consistent with the reduced steric bulk of the siloxyalkyl moiety in **3** in the group-transfer step.

Because the coupling product **5** is a radical precursor of the vinyl radical **4**, we examined the radical generation from **5** and subsequent C–C coupling reactions next. However, while alkyl tellurides are superior precursors for carbon-centered radicals,^[11] there are no reports on vinyl-radical generation from vinyl tellurides. We found that the tributyltin radical selectively cleaved the vinylic carbon–tellurium bond in **5** to generate the vinyl radical **4**, which could be used for further carbon–carbon bond formations (Scheme 3).^[12] Thus, treatment of (*E*)-**5a** with tributyltin hydride^[11a] in the presence of



Scheme 3. a) Bu_3SnH (1.2 equiv), azobisisobutyronitrile (AIBN) (0.1 equiv), 80°C , 1 h (no solvent); b) dimethyl fumarate (5 equiv), Bu_3SnH (2.4 equiv), AIBN (0.1 equiv), benzene, 80°C , 1 h (syringe pump addition of Bu_3SnH solution over 1 h); c) ethyl 2-tributylstannylmethylacrylate (3 equiv), AIBN (0.1 equiv), 80°C , 3 h (no solvent).

AIBN gave **7** in 92% yield. Because the stereochemical isomerization of vinyl radicals takes place very rapidly,^[13] the observed high *Z* stereoselectivity can be also ascribed to the selective hydrogen atom abstraction from **4**, which is stereoselective because of the bulky siloxyalkyl group. The vinyl radical **4a** also reacted with electron-deficient alkenes.^[11] Thus, treatment of (*E*)-**5a** with dimethyl fumarate in the presence of tributyltin hydride afforded the corresponding coupling product **8** ($\text{R}^3, \text{R}^4 = \text{CO}_2\text{Me}$; see Scheme 3) in good yield. The coupling of (*E*)-**5a** with ethyl 2-tributylstannylmethylacrylate also resulted in the desired coupling product **9** in good yield. In both cases, the olefinic stereochemistry of **5a** was highly preserved in the products.

In summary, we have developed a highly convergent and stereocontrolled synthesis of silylated allyl alcohols by domino, sequential radical-coupling reactions. Because the coupling reaction can be carried out with a variety of combinations of carbonyl compounds, alkynes, and agents to trap the vinyl radicals, this method provides a novel and powerful strategy for the diversity-oriented synthesis of allylic alcohols. Moreover, since the reaction does not require the use of a solvent, it also has the advantage of being environmentally friendly.^[14]

Received: December 14, 2001 [Z18386]

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- [10] CCDC 176516 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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From Vinyl Sulfides, Sulfoxides, and Sulfones to Vinyl Transition Metal Complexes**

Shahera Farhat and Ilan Marek*

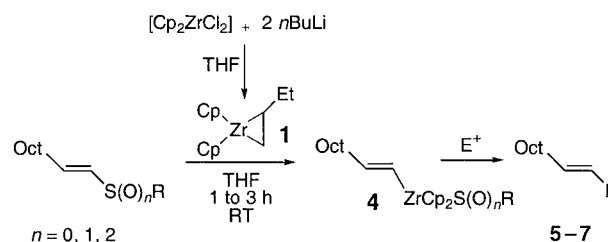
Numerous methods for the preparation of vinyl transition metal complexes are known and have been used frequently in organic synthesis.^[1] However, despite these widespread methods, there are still some impossible synthetic transformations. For example, the direct transformation of vinyl sulfones into vinylic organometallic derivatives is still unknown.^[2] The importance of the sulfone moiety stems from its application in carbon–carbon bond formation, and this in turn derives from key aspects of its properties and reactivity. In these applications the sulfone unit is simply a synthetic tool, which must almost always be disposed of at the end of the sequence.^[3] To date, the available methods fall roughly into three groups: those resulting in replacement of the sulfone by hydrogen (reductive desulfonylation),^[4] those in which sulfone removal is accompanied by C–C bond formation (alkylative desulfonylation),^[5] and finally those in which the sulfone is a good leaving group in β -elimination with formation of the sulfinic acid moiety (RSO_2^-).^[6]

Also unknown is the transformation of vinyl sulfoxides into vinylic organometallic derivatives, although sulfoxides are used in many settings, including asymmetric synthesis.^[3b] Only phenyl vinyl sulfide has been transformed into vinyl lithium derivatives through reductive metalation.^[7] This method involves the reductive lithiation of alkenyl phenyl sulfides by either a stoichiometric amount of the radical anion *p,p'*-di-*tert*-butylbiphenyl lithium (LDBB)^[7] or an excess of lithium metal in the presence of a catalytic amount of *p,p'*-di-*tert*-butylbiphenyl (DBB; 5 mol %).^[8] Such transformations failed with alkyl vinyl sulfides.^[7, 8] To fill these gaps new methods must still be found. In this communication, we report a new and general approach to these proposed transformations.

Recently we have been interested in the chemistry of low-valent zirconium and titanium species in organic synthesis,^[9] and we have found that bis(cyclopentadienyl)zirconacyclopentane **1** (easily prepared in situ by treatment of $[\text{Cp}_2\text{ZrCl}_2]$ with two equivalents of *n*-butyllithium, and known as the Negishi reagent)^[10, 11] is the reagent of choice for the stereoselective transformation of various enol ethers into vinyl zirconium derivatives.^[12] Based on this finding, we thought to apply this new concept to the previously described unknown transformation (sulfur-substituted alkenes into vinyl transition metal derivatives).

We were indeed very pleased to find that **1** reacts smoothly with (*E*)-decenyl phenyl sulfide **2**^[13] at room temperature in THF to give the vinyl zirconium complex **4** quantitatively

($n=0$, $\text{R}=\text{Ph}$, Scheme 1), as determined by analysis of a hydrolyzed aliquot containing an internal standard by gas chromatography. Hydrolysis of the reaction mixture gives the corresponding alkene **5** in 85% yield after purification (Table 1, entry 1).



Scheme 1. Stereoselective transformation of sulfur-substituted alkenes into vinyl zirconium derivatives. Oct = octyl. RT = room temperature. For the substituents see Table 1.

Table 1. Preparation of vinyl zirconium derivatives **4** from sulfur-substituted alkenes and subsequent reactions according to Scheme 1.

Entry	Starting compound	Electrophile	Product	Yield [%] ^[a]
1	Oct-CH=CH-SPh 2(E)	H_3O^+ (D_3O^+)	Oct-CH=CH-E 5 $\text{E}=\text{H}$ 6 $\text{E}=\text{D}$	85 (80)
2		I_2	Oct-CH=CH-I 7	78
3	Oct-CH=CH-SPr 3	H_3O^+	5	81
4		I_2	7	75
5	Oct-CH=CH-SPh (Z)-2	I_2	7	70
6	Oct-CH=CH-SPh (E)-12	I_2	7	75
7	Oct-CH=CH-SPh (Z)-12	I_2	7	63
8	Oct-CH=CH-SO ₂ Ph (E)-13a	H_3O^+	5	90
9		I_2	7	70
10	Oct-CH=CH-SO ₂ Tol 13b	H_3O^+	5	80
11	Oct-CH=CH-SO ₂ Me 13c	H_3O^+	5	86
12	Oct-CH=CH-SO ₂ Ph (Z)-13a	H_3O^+	5	89
13		I_2	7	75

[a] Yield of isolated product after purification by column chromatography.

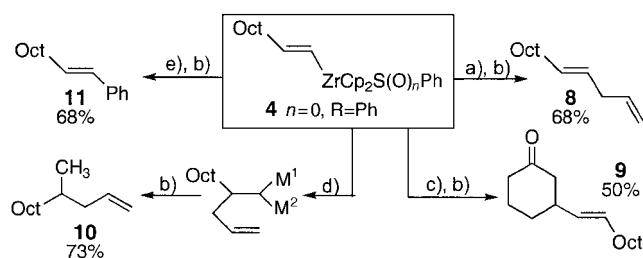
The formation of a discrete organometallic species was checked by deuterolysis and iodolysis of the reaction mixture (**6** and **7** in 80 and 78% yield, respectively, entries 1 and 2). The reaction also proceeds efficiently from the alkyl vinyl sulfide **3**, to give **5** and **7** in 81 and 75% yield, respectively, after hydrolysis and iodolysis (entries 3 and 4). When the reaction was performed on the (*Z*) isomer of aryl vinyl sulfide **2**, followed by addition of iodine, only the (*E*) vinyl iodide **7** was obtained (entry 5). Thus, the reaction is stereoselective and leads only to the (*E*) vinyl zirconium derivative.

[*] Prof. Dr. I. Marek, S. Farhat

Department of Chemistry and Institute of Catalysis Science and Technology
Technion-Israel Institute of Technology
Technion City, 32000 Haifa (Israel)
Fax: (+972) 4-829-37-09
E-mail: chilam@tx.technion.ac.il

[**] This research was supported by the Israel Science Foundation administrated by the Israel Academy of Sciences and Humanities, and by the Fund for the Promotion of Research at the Technion.

To further increase the scope of the reaction, transmetalation of the vinyl zirconium derivative **4** ($n = 0$, $R = Ph$) to give different vinylic organometallic derivatives was studied (Scheme 2).^[14] For example, the addition of a catalytic amount



Scheme 2. Transmetalation reactions of vinyl zirconium derivative **4** ($n = 0$, $R = Ph$) and further reactions. Reagents and conditions: a) 10% $CuCl/2LiCl$, allyl chloride; b) 1N HCl ; c) 10% $CuCl/2LiCl$, cyclohexenone, Me_3SiCl ; d) allylmagnesium bromide, $ZnBr_2$; e) 10% $CuCl/2LiCl$, 10% $[Pd(PPh_3)_4]$, PhI . $M^1, M^2 = MgBr, ZnBr$.

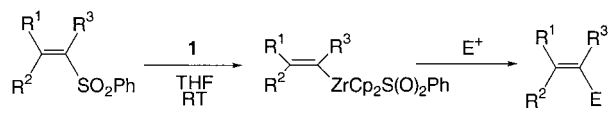
of $CuCl$ in the presence of $LiCl$ leads to the corresponding (*E*) vinyl copper derivative.^[15] This intermediate can react either by an S_N2' process with allyl chloride to give **8** (68% yield) or in a 1,4-addition with cyclohexenone in the presence of Me_3SiCl to give **9** (unoptimized yield 50%).^[15] The vinyl zirconium derivative can also be easily transformed in situ into the corresponding organobismetall derivative by the successive addition of allylmagnesium bromide and zinc dibromide.^[16] After hydrolysis **10** is obtained in 73% yield. Finally, the palladium-catalyzed cross-coupling reaction with phenyl iodide opens a new route for further functionalization as shown by the formation of **11**.^[17]

Vinyl transition metal derivatives are also easily obtained upon reaction of vinyl sulfoxides^[18] with two equivalents of **1**. Indeed, we found that the first equivalent of zirconacyclopentane **1** reduces the sulfoxides (*E*)-**12** and (*Z*)-**12** into the vinyl sulfides (*E*)-**2** and (*Z*)-**2**, respectively, in one hour at room temperature with concomitant formation of solid $[Cp_2Zr=O]_n$.^[19] This unexpected, mild reduction^[20] occurs without isomerization of the double bond.^[21] When the newly formed phenyl vinyl sulfides **2** are treated in situ with a second equivalent of **1**, the organometallic derivative **4** ($n = 0$, $R = Ph$; and (*E*)-**7** after iodinolysis) forms with complete isomerization of the double bond (see Table 1, entries 6 and 7) in analogy to the previous reactions (entries 1 and 5).

Finally, we turned our attention to vinyl sulfoxides.^[4, 5] We first tested the effect of the *R* group on the elimination of the sulfinate moiety in our sequence (Table 1, entries 8, 10, 11).^[22] Regardless of the *R* group of the sulfone—phenyl (**13a**), tolyl (**13b**), or methyl (**13c**)—we observed a very fast transformation of the (*E*) vinyl sulfone into the corresponding vinylic organometallic derivatives **4** and then **5** after hydrolysis in excellent yields. By reaction with iodine (*E*)-**13a** gives the pure *trans* vinyl iodide **7** in 70% yield (entry 9). Again, the (*Z*) isomer of vinyl sulfone **13a** undergoes complete isomerization in this process and gives only the (*E*) isomer, **7**, in good yield (entry 13).

The scope of this reaction is even broader since the transformation of vinyl sulfoxides into vinyl transition metal

complexes can be generalized to polysubstituted olefins, as described in Scheme 3 and Table 2. Although the yield decreases slightly, as expected, with the degree of substitution



Scheme 3. Synthesis of polysubstituted vinyl zirconium derivatives and further reactions. For the substituents see Table 2.

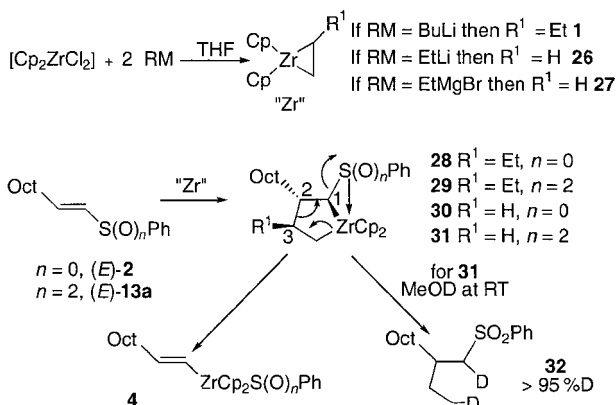
Table 2. Preparation of vinyl zirconium derivatives from polysubstituted vinyl sulfoxides and subsequent reactions according to Scheme 3.

Entry	Starting compound	Electrophile	Product	Yield [%] ^[a]
1		H_3O^+		70
2		$MeOD$		60
3		H_3O^+		64
4		H_3O^+		68
5		I_2		67
6		H_3O^+		70
7		H_3O^+		48

[a] Yield of isolated product after purification by column chromatography. [b] As a 1:1 mixture of geometrical isomers.

of the starting vinyl sulfone (cf. entries 1–6 to entry 7 of Table 2), the reaction proceeds smoothly in all cases. When the reaction is performed on β,β -disubstituted vinyl sulfoxides **14**–**16**, good overall yields are obtained (see entries 1–5). However, the quenching of the resulting vinyl zirconium derivatives with I_2 leads to two isomers in a 1:1 ratio (entry 5). On the other hand, when the α,β -disubstituted vinyl sulfone **17** is treated with **1**, a single (*E*) isomer, **24**, is obtained after hydrolysis (entry 6). Even a tetrasubstituted alkene such as **18** is easily transformed into the corresponding vinylic organometallic derivative and then into **25** after acidic treatment (entry 7).

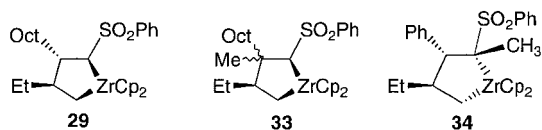
Although further investigations are needed to elucidate completely the mechanism of this reaction, it possibly involves the carbozirconation of the heterosubstituted double bond by zirconocene **1** to lead to the unstable functionalized zirconacycles **28** and **29** (Scheme 4). Although we were not able to trap **28** and **29** as intermediates (only complex **4**, $R = Ph$, could be isolated), **30** and **31**^[23] were isolated in moderate yields when the same reaction was repeated with **26** Li and **27**



Scheme 4. Mechanistic rationalization of the isomerization and elimination in the reactions shown in Scheme 3.

MgBr, respectively (Scheme 4). Deuterolysis and hydrolysis of **31** yielded **32** and its hydrogen analogue, respectively. Decarbozirconation of **30** and **31** occurs with elimination of the leaving group to give the corresponding vinylic organometallic derivative **4**, $R = Ph$. This reaction seems to proceed through skeletal rearrangement,^[24] since the zirconacycle intermediate disappears in favor of the vinyl transition metal complex, which is obtained in very good yield. In this case, whatever the stereochemistry of the starting olefin (as described in Tables 1 and 2), the carbon–heteroatom bond of the metalated center C^1 shifts to produce the most stable intermediate (see **28–31** in Scheme 4). Such an isomerization could be caused by an interaction between the sulfur moiety and the zirconium atom,^[25] which would weaken the $C^1\text{–Zr}$ bond and facilitate the isomerization. Then, whatever the stereochemistry of the starting material, a conformation is always possible in which the $C^1\text{–S}$ bond is antiperiplanar to the $C^2\text{–C}^3$ bond (see **28–31**, Scheme 4). The elimination reaction (or decarbozirconation) occurs in a concerted way to give the vinyl zirconium compound.

The stereochemistry of the vinyl zirconium complex can then be rationalized by the zirconacyclopentane intermediates **29**, **33**, and **34**. Indeed, in **29** the most stable isomer is



expected to have an *anti* relationship between the octyl substituent and the zirconium atom. When one more substituent is added in the β -position, as in **16**, intermediate **33** leads to two isomeric vinyl zirconium derivatives in a 1:1 ratio (see Table 2, entry 5). However, when **17** is treated with **1**, **34** is expected to be the more stable zirconacycle as a result of the steric interaction between the phenyl and the alkyl groups.^[26]

In summary, we have developed an easy and general new method for the conversion of vinyl sulfides, sulfoxides, and sulfones into vinylic organozirconium derivatives with good yields of isolated products. Our investigations of several

different systems as well as of a catalytic process in zirconium are currently in progress.

Experimental Section

A solution of *n*-butyllithium in hexanes (1.6 M, 3.3 equiv) was added slowly to a solution of bis(cyclopentadienyl)zirconium dichloride (1.5 equiv) in dry THF at -78°C . After the solution had been stirred for 1 h at -78°C , vinyl sulfide, sulfoxide, or sulfone was added (1 equiv) at -78°C . The reaction mixture was allowed to warm to room temperature and stirred for 2.5–5 h. The quantitative formation of the adduct **4** was checked by gas chromatography. Then, the solution was cooled to -20°C and the electrophile was added. The reaction mixture was warmed to room temperature and diluted with ether and 1 N HCl. The aqueous phase was then extracted three times with ether. The combined organic phases were washed successively with a solution of saturated aqueous sodium hydrogen carbonate, brine, and water (in case of addition of iodine, aqueous $Na_2S_2O_3$ was also used), dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue obtained was finally purified by column chromatography on silica gel.

Received: November 2, 2001
Revised: January 21, 2002 [Z18150]

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Polymeric Surfactants for the New Millennium: A pH-Responsive, Zwitterionic, Schizophrenic Diblock Copolymer**

Shiyong Liu and Steven P. Armes*

Recently, we have demonstrated that certain hydrophilic AB diblock copolymers can self-assemble in aqueous media to form both conventional micelles (with the A block forming the micelle core) and reverse micelles (with the B block forming the micelle core),^[1–3] and we have described these diblock copolymers as having “schizophrenic” character.^[3] To date, only two well-documented examples of schizophrenic

diblock copolymers have been reported. The first “proof-of-concept” example was reported by Büttin et al. who polymerized 2-(*N*-morpholino)ethyl methacrylate (MEMA), followed by 2-(diethylamino)ethyl methacrylate (DEA) using group-transfer polymerization (GTP).^[1, 2] The two micellar transitions of this polymer were induced by changes in solution pH and ionic strength, respectively. In both cases micellization occurred at around 20 °C, but the addition of large quantities of electrolyte (1.0 M Na₂SO₄) to produce MEMA-core micelles was somewhat artificial. The second example involved using a poly(propylene oxide)-based (PPO) macro-initiator for the polymerization of DEA by atom-transfer radical polymerization (ATRP) in alcoholic media at 55 °C. The resulting PPO–DEA diblock copolymer dissolved in cold water at pH 6.5. DEA-core micelles were formed at 5 °C in mildly alkaline solution (pH 8.5) and PPO-core micelles were obtained at pH 6.5 at elevated temperatures (40–70 °C). Thus, neither micellar state was stable at ambient temperature; this is rather inconvenient for characterization purposes and, more importantly, for industrial applications of this particular polymeric surfactant.

Herein we describe a new zwitterionic AB diblock copolymer that undergoes spontaneous self-assembly in aqueous solution at ambient temperature to form both micelles and reverse micelles, simply by switching the solution pH (Figure 1). This remarkable diblock copolymer is poly(4-vinyl benzoic acid-*block*-2-(diethylamino)ethyl methacrylate) (VBA-*b*-DEA), which was synthesized by ATRP using protecting group chemistry, followed by hydrolysis; the degrees of polymerization of the VBA and DEA blocks are 60 and 66, respectively (for experimental details, see Supporting Information).

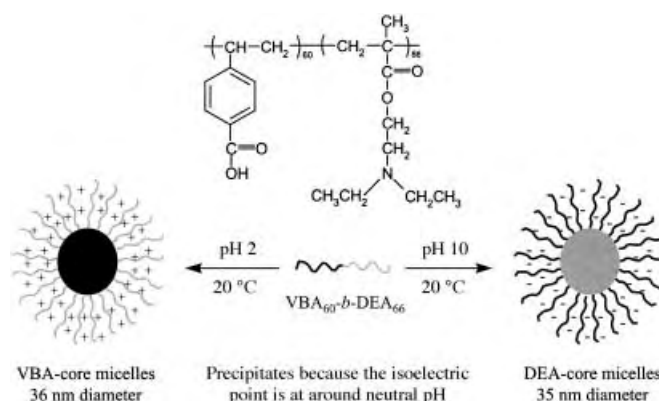


Figure 1. Chemical structure of VBA₆₀-*b*-DEA₆₆ diblock copolymer and its pH-induced “schizophrenic” micellization behavior in aqueous solution.

It is known that DEA homopolymer is a weak polybase with a pK_a of approximately 7.3.^[4] DEA homopolymer dissolves in acid as a cationic polyelectrolyte, by protonation of its amine groups, but becomes insoluble above pH 7.1. VBA homopolymer has a pK_a of around 7.1 (determined by hydrogen ion titration); it is insoluble at low pH but becomes soluble as an anionic polyelectrolyte above pH 6.2, by ionization of its carboxylic acid groups. Hence, the VBA-*b*-DEA diblock copolymer is a more hydrophobic analogue of

[*] Prof. S. P. Armes, Dr. S. Liu
School of Chemistry, Physics and Environmental Science
University of Sussex
Falmer, Brighton, E. Sussex, BN1 9QJ (UK)
Fax: (+44) 1273-677-196
E-mail: s.p.arnes@sussex.ac.uk

[**] We thank the EPSRC for a post-doctoral fellowship for S.Y.L. (GR/N17409).

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

the extensively reported poly(2-(dimethylamino)ethyl methacrylate)-*block*-(methacrylic acid)) zwitterionic diblock copolymer.^[5–15] Depending on its block composition, and on the ionic strength and pH of the aqueous solution, the latter diblock copolymer is either soluble,^[5, 12–13] insoluble, or forms large, nonmicellar aggregates of 400–500 nm diameter.^[11] In contrast, the VBA-*b*-DEA diblock copolymer reported herein was expected to form compact, well-defined VBA-core micelles at low pH and DEA-core micelles at high pH (Figure 1). Dynamic and static light scattering, ¹H NMR spectroscopy, aqueous electrophoresis, transmission electron microscopy, surface tensiometry, and fluorescence techniques were used to characterize the aqueous-solution properties of this unique zwitterionic diblock copolymer.

Figure 2 shows the ¹H NMR spectra of the protected diblock copolymer before hydrolysis (spectrum a) and after hydrolysis (spectrum b). In its deprotected, zwitterionic form there are very few organic solvents for the VBA-*b*-DEA

diblock copolymer. Fortunately, it proved to be sufficiently soluble in [D₅]pyridine. In this basic solvent, the DEA block is in its neutral form and the VBA block is ionized (carboxylate salt form). The poly(*tert*-butyl 4-vinylbenzoate) block is efficiently hydrolyzed to form poly(4-vinylbenzoic acid). Moreover, before and after hydrolysis, the DEA content of the diblock remains constant within experimental error, which indicates that no unwanted hydrolysis of the DEA residues occurred during removal of the *tert*-butyl protecting groups.

The deprotected VBA₆₀-*b*-DEA₆₆ diblock copolymer dissolves in either dilute acidic or dilute alkaline solution. After initial dissolution at high or low pH, a 1.0 g L⁻¹ solution of this copolymer precipitated between pH 6.6–8.3. In principle, such precipitation should be confined to a discrete, well-defined pH value known as the isoelectric point (IEP), at which the cationic charge on the DEA block just balances the anionic charge on the VBA block.^[5–15] In practice, a pH range is usually observed rather than a single value; this maybe because of polydispersity effects. Below pH 6 or above pH 9, the zwitterionic diblock copolymer redissolved to form a bluish or transparent micellar solution. Because the calculated IEP^[5] is 7.25, this pH-dependent solubility is in good agreement with the respective pK_a and pK_b values of the VBA and DEA blocks; it is also consistent with the observations of several research groups who have studied related zwitterionic diblock copolymers.^[5–15]

In Figure 2, spectrum c, aromatic signals corresponding to the VBA block are evident at $\delta = 6.3–7.8$, but there are no signals corresponding to the DEA residues, which indicates that DEA-core micelles with anionic VBA coronas are formed at pH 10, as expected. However, in spectrum d, all of the characteristic signals arising from the DEA residues are visible but there are no signals corresponding to the aromatic VBA block; this indicates that VBA-core micelles with cationic DEA coronas are formed at pH 2.

Figure 3a shows the variation of averaged hydrodynamic diameter ($\langle D_h \rangle$) on adjusting the pH of a 1.0 g L⁻¹ VBA₆₀-DEA₆₆ diblock-copolymer aqueous solution. At pH 2, well-defined VBA-core micelles are formed with a $\langle D_h \rangle$ of 36 nm and a polydispersity of 0.15. As the pH is increased, the micelle diameter increased monotonically because of the concomitant decrease in degree of protonation of the DEA block and increasing degree of ionization of the VBA block. Thus, as the solubility of the VBA block increases and the DEA block becomes less hydrophilic, the overall hydrophilic–hydrophobic balance of the diblock copolymer changes and larger, nonmicellar aggregates^[11, 16–20] are formed at around pH 6 with a $\langle D_h \rangle$ of about 120 nm. A further increase in pH leads to precipitation, indicated by the dramatic increase in turbidity (see shaded region, Figure 3). Above pH 8.5, the solution becomes transparent again. At pH 9.2, colloidal aggregates are formed with a $\langle D_h \rangle$ of around 66 nm. Well-defined, compact DEA-core micelles with a mean diameter of 35 nm are formed at pH 10. The polydispersities of micelles formed in alkaline media ranged from 0.1–0.2.

Aqueous electrophoresis studies (Figure 3b) indicate that the net charge on the particles is close to zero at pH 7.5; this IEP is very close to the midpoint of the precipitation region,

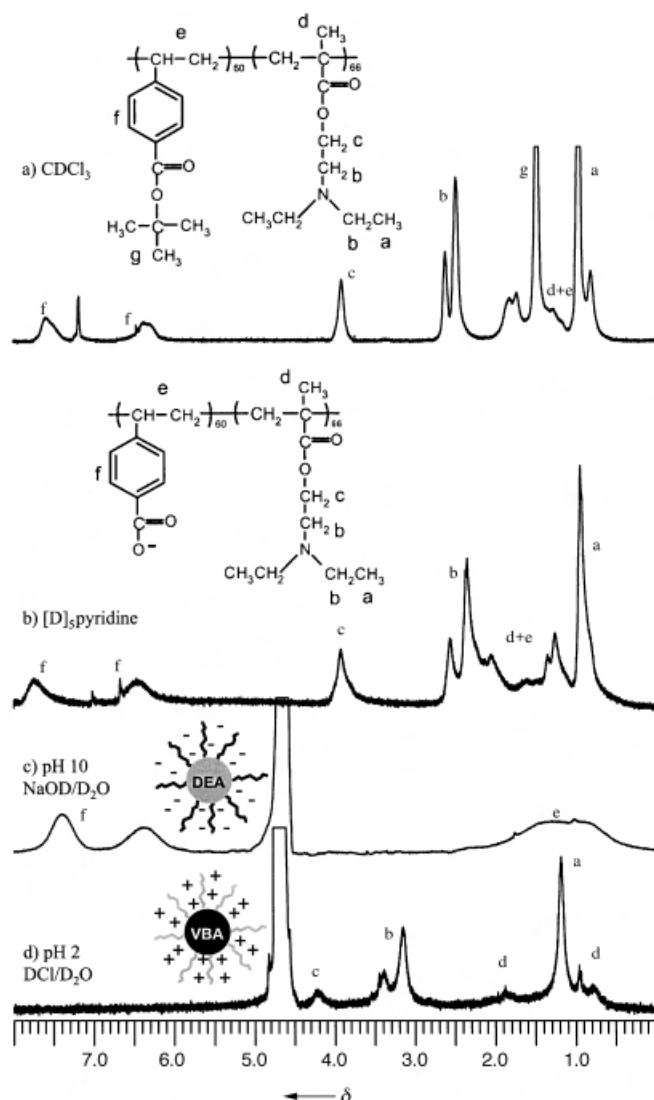


Figure 2. ¹H NMR spectra obtained for a) the *t*BuVBA₆₀-*b*-DEA₆₆ precursor diblock copolymer in CDCl₃; b) after hydrolysis in [D₅]pyridine (note the disappearance of the signal at 1.5 ppm, caused by the removal of the *t*Bu protecting groups); c) DEA-core micelles formed at pH 10; d) VBA-core micelles formed at pH 2.

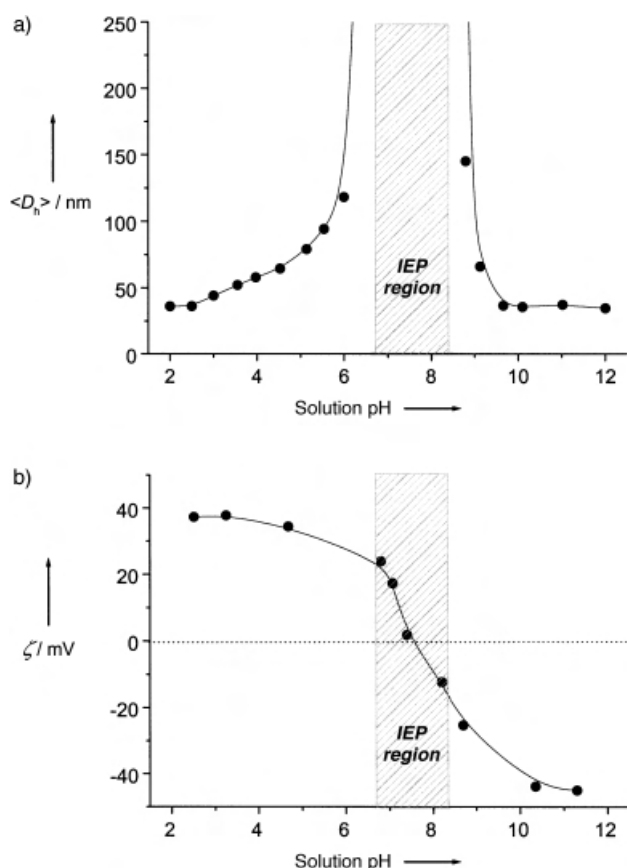


Figure 3. a) The variation of hydrodynamic micelle diameter as a function of solution pH for a dilute aqueous solution (1.0 g L^{-1}) of the $\text{VBA}_{60}\text{-}b\text{-DEA}_{66}$ diblock copolymer at 20°C . b) The variation of zeta potential as a function of pH for a 1.0 g L^{-1} aqueous solution of the $\text{VBA}_{60}\text{-}b\text{-DEA}_{66}$ zwitterionic diblock copolymer at 20°C .

as determined by visual inspection (pH 7.4). Either side of this IEP, the micelles had either positive zeta potentials because of cationic DEA coronas (at low pH) or negative zeta potentials because of anionic VBA coronas (at high pH).

Static light-scattering studies (Zimm analysis) for VBA-core micelles and DEA-core micelles, formed at pH 2 and pH 10, respectively, yielded weight-average micelle masses of approximately 1.45×10^6 and $2.25 \times 10^6 \text{ g mol}^{-1}$. The corresponding micelle aggregation numbers (N_{agg}) were estimated to be 46 and 72, respectively (see Table 1). By use of $\langle \rho \rangle = M_w / (4\pi \langle R_h \rangle^3 / 3)$, where R_h is the hydrodynamic radius, the average densities $\langle \rho \rangle$ of the VBA-core and DEA-core micelles were estimated to be 0.11 and 0.15 g cm^{-3} , respectively. Thus, the average density of the VBA-core micelles is somewhat higher

Table 1. Static and dynamic light-scattering data obtained for the two types of micelles formed by the “schizophrenic” $\text{VBA}_{60}\text{-}b\text{-DEA}_{66}$ diblock copolymer in water at 20°C .

Conditions	DEA-core micelles at pH 10	VBA-core micelles at pH 2
$M_{w, \text{micelles}}$	1.45×10^6	2.25×10^6
$\langle R_g \rangle [\text{nm}]$	16.5	14.7
$\langle R_h \rangle [\text{nm}]$	17.5	18
$\langle R_g \rangle / \langle R_h \rangle$	0.94	0.82
N_{agg}	46	72
$\langle \rho \rangle [\text{g cm}^{-3}]$	0.11	0.15

than that of the DEA-core micelles. The $\langle R_g \rangle / \langle R_h \rangle$ ratio, where R_g is the radius of gyration, follows a similar trend, with the value of 0.82 obtained for the VBA-core micelles lying closer to the theoretical value of 0.774 for a hard sphere. However, these average micelle densities are much lower than the solid-state density of 1.28 g cm^{-3} , determined for the $\text{VBA}_{60}\text{-}b\text{-DEA}_{66}$ diblock copolymer by helium pycnometry. This result indicates that both types of micelles are appreciably swollen, which suggests significant stretching of the polyelectrolyte chains in the micelle corona.

Transmission electron microscopy (TEM) studies of both types of micelles (Figure 4) indicated spherical morphologies, with mean number-average diameters of about 25 nm and

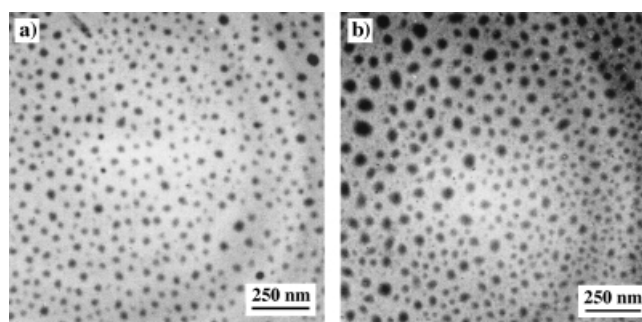


Figure 4. Typical TEM micrographs of a) DEA-core micelles at pH 10 and b) VBA-core micelles at pH 2, prepared using the $\text{VBA}_{60}\text{-}b\text{-DEA}_{66}$ schizophrenic diblock copolymer. The micelles were stained with RuO_4 vapor to enhance contrast.

40 nm for DEA-core and VBA-core micelles, respectively. The DEA-core micelles have a fairly uniform size-distribution and, taking into account both the degree of hydration and polydispersity effects, the mean diameter determined by TEM compares reasonably well to that from dynamic light scattering (DLS). TEM studies of the VBA-core micelles indicated that these micelles are somewhat more polydisperse, with diameters ranging from 20–70 nm; these values should be compared to the $\langle D_h \rangle$ of 36 nm obtained by DLS. This discrepancy may indicate some degree of spreading of these micelles on the surface of the TEM grid; such “flattening” has recently been observed for similar micelles with cationic coronas adsorbed at a planar mica surface.^[21]

Such micellar self-assembly is fully reversible for many cycles, provided that the additional background salt formed during pH adjustment does not cause salting out (which typically occurs at around 0.8 M NaCl). However, the mean micelle diameter increases gradually at higher salt concentrations, because the insoluble block becomes more hydrophobic and the soluble block less hydrophilic. Surface tension and fluorescence studies of the block copolymer micelles are summarized in the Supporting Information.

In summary, a new zwitterionic diblock copolymer has been synthesized by ATRP, which exhibits a rich phase behavior in aqueous solution at 20°C . Depending solely on the solution pH, this “schizophrenic” copolymer can exist in two different micellar states and also exhibits an isoelectric point at around neutral pH. This novel zwitterionic diblock copolymer may

have potential applications as a pigment dispersant,^[10, 22, 23] or in the separation and purification of proteins.^[7, 24]

Received: November 26, 2001 [Z18276]

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A Selective Chromogenic Reagent for Nitrate**

Félix Sancenón, Ramón Martínez-Máñez,* and Juan Soto

The selective sensing of anions by natural and synthetic receptors is an important area of supramolecular chemistry.^[1] Anions play significant roles in biological and environmental processes, therefore the development of new chemosensors for anions is an important topic. Anion-sensing receptors incorporate into their structures groups that are capable of interaction with anions, and sensing subunits in which spectroscopic^[2] or electrochemical^[3] features change upon anion binding. Chemosensors with changes in their spectroscopic behavior have either fluorogenic^[4] or chromogenic^[5] signalling subunits. Chromogenic reagents are especially attractive because the anion determination can be carried out by the naked eye, without the use of expensive equipment. Chromogenic reagents for the selective detection of inorganic and organic anions have been reported.^[6] However, it is still a challenge to find chromogenic receptors for the selective sensing of poorly coordinating anions such as nitrate. As far as we know, the only example of nitrate sensing by color change, by use of receptors coupled to dyes, was reported recently, and it involved a competitive assay between nitrate and methyl red or resorufin in binding a polyamide cage, in dichloromethane:methanol 50:50 v/v. The system, however, is not specific and addition of bromide or perchlorate also produced color changes, although to a lesser extent.^[7] We now report a new and specific chromogenic reagent for nitrate using a *p*-nitrophenylazobenzene group as a dye and a mercuric complex as an anion-binding site. The system shows a selective change of color in acetonitrile but can also be applied to the selective determination of nitrate in water.

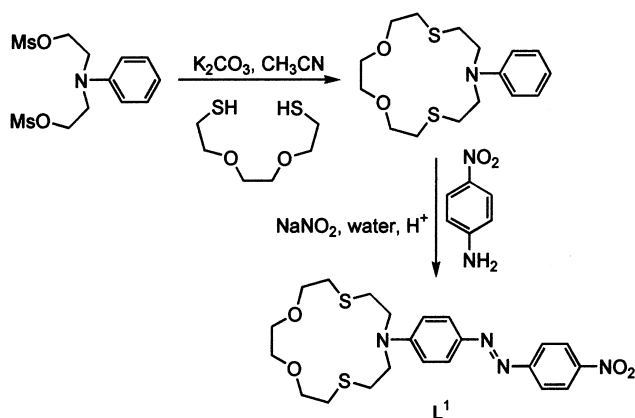
The aza-oxa-thia macrocycle (see Scheme 1) was obtained by the cyclization of 3,6-dioxa-1,8-octanedithiol and dimesylated *N,N*-diethanolphenylamine in acetonitrile/K₂CO₃ at reflux,^[8] under high dilution conditions. The macrocycle was obtained in a 40 % yield. The macrocycle was coupled with the azonium salt of *p*-nitroaniline in HCl to obtain **L**¹ as a red-orange powder (80 % yield). ¹H NMR and ¹³C NMR spectroscopy, mass spectrometry, and elemental analysis are consistent with the proposed formulation.

The visible spectrum of the ligand **L**¹ in acetonitrile is characterized by an intense band centered at 490 nm ($\epsilon = 26000 \text{ M}^{-1} \text{ cm}^{-1}$), which is responsible for the orange color of the solutions and is caused by a charge transfer from the

[*] Dr. R. Martínez-Máñez, F. Sancenón, Dr. J. Soto
Departamento de Química
Universidad Politécnica de Valencia
Camino de Vera s/n, 46071 Valencia (Spain)
Fax: (+34) 96-387-9349
E-mail: rmaez@qim.upv.es

[**] This research was supported by the Ministerio de Ciencia y Tecnología (proyecto PB98-1430-C02-02, 1FD97-0508-C03-01, and AMB99-0504-C02-01). F.S. also thanks the Ministerio de Ciencia y Tecnología for a Doctoral Fellowship.

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



Scheme 1. Synthesis of **L**¹.

donor nitrogen atom of the macrocycle to the acceptor nitro moiety.^[9] No changes were observed in the UV/Vis spectrum in acetonitrile, upon addition of one equivalent of Li⁺, Na⁺, K⁺, Ca²⁺, Ba²⁺, and Mg²⁺ (perchlorate salts) or upon addition of up to 100 equivalents of the anions F[−], Cl[−], Br[−], I[−], H₂PO₄[−], HSO₄[−], and NO₃[−] (tetra-*N*-butylammonium salts). Whereas the addition of the metal ions Ni²⁺, Zn²⁺, Cd²⁺, Pb²⁺, Fe²⁺, and Ag⁺ did not have any significant effect, the presence of Cu²⁺, Hg²⁺, and Fe³⁺ cations induced a red shift of the **L**¹ visible band to 520–540 nm, which resulted in a color change of the solution from orange to red. The 520 nm band intensity (concentration of **L**¹ 1.0 × 10^{−4} M in acetonitrile) was monitored upon addition of the metal ions Cu²⁺, Hg²⁺, and Fe³⁺, which allowed us to determine complex stability constants. Titration of **L**¹ with Cu²⁺ indicated the formation of 1:1 ligand-to-metal complexes. The log *K* value for the complex-formation equilibrium, calculated through nonlinear least-squares treatment of the titration profiles,^[10] was 5.9 ± 0.2. For Hg²⁺ and Fe³⁺ ions, the titration data suggested the formation of sandwichlike complexes with 2:1 ligand:metal stoichiometries. Calculated log *K* values were 11.2 ± 0.3 and 10.9 ± 0.2 for the formation of the [Hg(**L**¹)₂]²⁺ and [Fe(**L**¹)₂]³⁺ complexes, respectively. Additional ¹H and ¹³C NMR spectroscopic studies were carried out on the Hg²⁺–**L**¹ system. NMR spectroscopy confirmed the formation of the 1:2 metal:ligand complex [Hg(**L**¹)₂]²⁺ with significant shifts of the signals arising from the protons and carbons of the **L**¹ aza-oxa-thia ring, in the presence of the mercuric cation.

These [Cu(**L**¹)]²⁺, [Hg(**L**¹)₂]²⁺, and [Fe(**L**¹)₂]³⁺ complexes have proved to be suitable chromogenic receptors for anion sensing. Thus, changes in the visible spectrum were recorded in acetonitrile solutions of these receptors upon addition of F[−], Cl[−], Br[−], I[−], H₂PO₄[−], HSO₄[−], and NO₃[−] ions. Each complex showed quite different behavior in the presence of the anions studied, the most remarkable effect being observed with the [Hg(**L**¹)₂]²⁺ complex. Hence, while addition of every anion to the [Cu(**L**¹)]²⁺ complex solution resulted in a shift of the visible band of the complex and color change (the color variation is more remarkable for F[−], Cl[−], I[−], H₂PO₄[−], and NO₃[−] ions than Br[−] and HSO₄[−] ions, see Supporting Information), the [Fe(**L**¹)₂]³⁺ and [Hg(**L**¹)₂]²⁺ complexes showed a more selective response. For [Fe(**L**¹)₂]³⁺, only addition of I[−] and NO₃[−] ions resulted in a shift of the

540 nm band to 490 nm with a concomitant change in color from red to yellow, whereas the [Hg(**L**¹)₂]²⁺ complex gave a specific response to NO₃[−] ions, as this was the only anion which produced a color change of the receptor solution (Figure 1). Competitive experiments have been carried out using the [Hg(**L**¹)₂]²⁺ complex. The same spectral variation was found upon nitrate addition in solutions containing a five-fold excess of chloride, bromide, iodide, or sulfate. In contrast, some interference was detected in the presence of an excess of fluoride or phosphate.

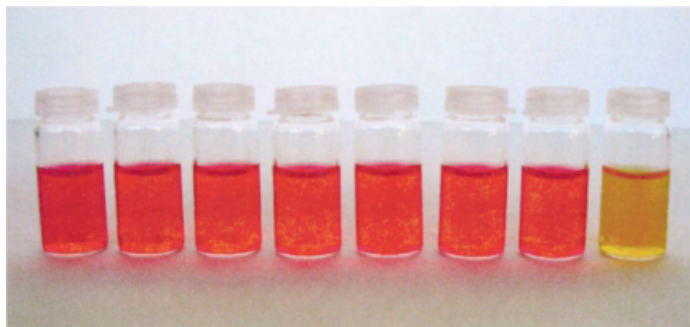


Figure 1. Color changes induced in [Hg(**L**¹)₂]²⁺ (9.6 × 10^{−5} mol dm^{−3}) in acetonitrile. From left to right: no anion, F[−], Cl[−], Br[−], I[−], H₂PO₄[−], HSO₄[−], and NO₃[−].

Titration of acetonitrile solutions of the complexes [Cu(**L**¹)]²⁺, [Hg(**L**¹)₂]²⁺, and [Fe(**L**¹)₂]³⁺ by addition of aliquots of the corresponding anion solution gave isosbestic points in all cases, which indicate the formation of 1:1 anion:receptor complexes. From the titration data, stability constants for the formation of anion–receptor complexes were determined (Table 1).^[10] The receptor [Cu(**L**¹)]²⁺ forms strong complexes with all the anions studied. Stability constants are in the order F[−] > H₂PO₄[−] > NO₃[−] > Cl[−] = I[−] > HSO₄[−] = Br[−]. The [Hg(**L**¹)₂]²⁺ and [Fe(**L**¹)₂]³⁺ receptors, though they show a more selective response, also form strong complexes with values of the stability constants of the same order of those of the copper receptor.

Table 1. Stability constants from titration experiments in acetonitrile for the formation of 1:1 anion:receptor complexes.^[a]

	NO ₃ [−]	F [−]	Cl [−]	Br [−]	I [−]	HSO ₄ [−]	H ₂ PO ₄ [−]
[Cu(L ¹)] ²⁺	6.2(2)	7.5(5)	4.7(1)	3.4(1)	4.6(2)	3.7(1)	7.1(2)
[Fe(L ¹) ₂] ³⁺	5.7(1)	–	–	–	4.8(1)	–	–
[Hg(L ¹) ₂] ²⁺	6.2(2)	–	–	–	–	–	–

[a] Values in parentheses are the standard deviations in the last significant digit.

These results show that dye-containing metal complexes can act as efficient and selective chromogenic reagents for anion sensing.^[11] Additionally, there is a remarkable control of the selectivity by simple selection of the metal cation. Thus, metal ions such as Fe³⁺, Cu²⁺, and Hg²⁺ are able to change the color of the dye **L**¹ probably by a suitable coordination with the aza-oxa-thia ring. In fact, Fe³⁺, Cu²⁺, and Hg²⁺ ions, among the metals studied, give the strongest complexes with amines and therefore an effective coordination between the metals and the nitrogen atom of the aza-oxa-thia ring of the dye

would be expected.^[12] This interaction causes the disappearance of the **L**¹ charge-transfer band and the appearance of a new red-shifted band that probably arises from a new charge-transfer transition, in which orbitals of the metal centers are involved. This metal–dye interaction is very sensitive to local electronic disturbances produced by the presence of the anions and hence, coordination or formation of ion-pairs between certain anions and [Cu(**L**¹)]²⁺, [Hg(**L**¹)₂]²⁺, and [Fe(**L**¹)₂]³⁺ receptors could induce the observed color changes. NMR spectroscopic studies of the [Hg(**L**¹)₂]²⁺–nitrate system showed a slight shift of the signals assigned to the protons *ortho* to the azo group, in the presence of nitrate ions. This shift could be related to the presence of π -stacking interactions between the nitrate ion and the *p*-nitrophenylazobenzene group. Therefore, as both the nitrate anion and the **L**¹ molecule are planar, and nitrate forms equally strong complexes with all three receptors [Cu(**L**¹)]²⁺, [Hg(**L**¹)₂]²⁺, and [Fe(**L**¹)₂]³⁺, we suggest that the interaction between the NO₃[−] ions and the receptors must proceed through the **L**¹ molecule and not through the cationic metal center. Hence, though the interaction between nitrate and the receptors must be favored by electrostatic forces, π -stacking interactions between the planar nitrate and the also planar *p*-nitrophenylazobenzene could be responsible for the color changes observed in the presence of nitrate.

The selective nitrate sensing using the [Hg(**L**¹)₂]²⁺ complex is a remarkable effect, thus some preliminary studies were carried out to use this color change as a method for direct nitrate determination in water. We realized that the addition of small quantities of water (up to 0.5%) to acetonitrile solutions of [Hg(**L**¹)₂]²⁺ did not have any effect in the selective color change from red to yellow observed in the presence of nitrate. Therefore, using a calibration curve for nitrate in an acetonitrile:water solution (Figure 2), nitrate concentration in aqueous solutions can be approximately determined by the addition of small aliquots of aqueous nitrate ions (few μ L) to solutions of the [Hg(**L**¹)₂]²⁺ complex in acetonitrile. By this method, the concentration of nitrate in the 20–200 ppm range was determined in the presence of other anions (carbonate,

sulfate, chloride, calcium, magnesium, and sodium in typical concentration ranges 1×10^{-3} – 5×10^{-4}). Table 2 shows the nitrate concentration in water determined by addition of 50 μ L of the aqueous sample to 10 mL of acetonitrile solutions of [Hg(**L**¹)₂]²⁺ and further measurement of the absorption band. The method is easy to carry out and allows colorimetric determination of nitrate in the presence of the other anions and cations typically present in water. We also found that lower concentrations of nitrate can also be determined by the simple preconcentration of diluted aqueous samples.

Table 2. Concentration of nitrate ($-\log [\text{NO}_3^-]$) in different samples of water.

Real concentration	Determined ^[a] with [Hg(L ¹) ₂] ²⁺
2.36	2.40
2.66	2.70
3.02	3.10
3.43	3.50

[a] Concentration of nitrate was determined using the calibration curve (Figure 2).

In conclusion, Cu²⁺, Fe³⁺, and Hg²⁺ complexes with the receptor **L**¹ are very sensitive to the electronic perturbations produced by anions and have proved to be suitable chromogenic reagents for anion sensing. The selective detection of the poorly coordinating anion nitrate, and the possibility of its direct quantification in water using a simple color change are especially significant. These findings might open up new opportunities in the chromogenic sensing of traditionally poorly coordinating anions by synthetic receptors.

Received: December 7, 2001 [Z18347]

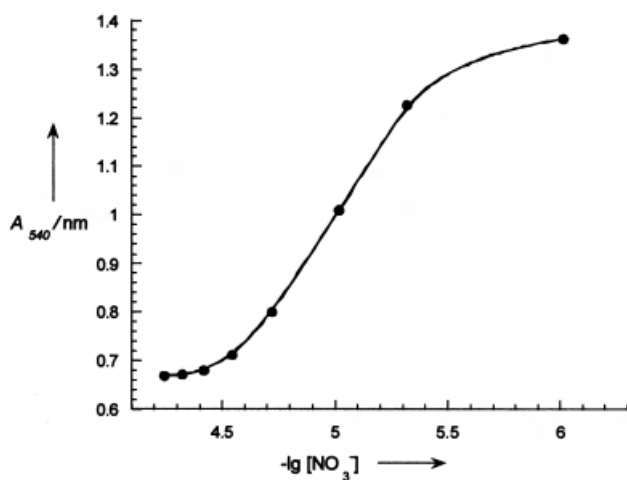


Figure 2. Calibration curve used to determine nitrate concentration in water. Absorption (A) versus logarithm of the nitrate concentration in acetonitrile:water 99.5:0.5 v/v. Concentration of [Hg(**L**¹)₂]²⁺: 9.6×10^{-5} mol dm^{−3}.

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Selective Recognition of Fluoride Anion Using a Li⁺–Metallacrown Complex

Marie-Line Lehaire, Rosario Scopelliti, Holger Piotrowski, and Kay Severin*

With the final goal of constructing specific chemosensors for fluoride anions, considerable efforts have been put into the synthesis of compounds that are able to bind fluoride ions with high affinity and selectivity. The receptors described include organic macrocycles with convergent H-bond donor groups and compounds containing Lewis acidic boron, silicon, or tin atoms.^[1, 2] Here we report a conceptually new fluoride receptor, the basic principle of which is shown in Figure 1. A lithium ion, which serves as a binding site, is coordinated

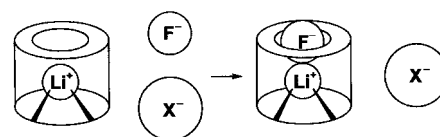


Figure 1. Schematic representation of a selective fluoride receptor with a Li⁺ ion binding site.

inside a three-dimensional host compound. The accessibility of the Li⁺ center is controlled by the steric requirements of the host: the small fluoride anion is able to enter the cavity whereas larger anions are efficiently blocked. Since the radius of the fluoride ion is significantly shorter than that of most other anions,^[1b] a highly specific receptor is obtained.

The utilization of the hard acid Li⁺ ion for the binding of the hard base F[−] appears to be very attractive, but so far Li⁺-based fluoride receptors have not been described. In fact, there is not even structural data available on complexes containing molecular LiF,^[3, 4] although numerous examples of other alkali metal halide complexes are known. The difficulty of stabilizing molecular LiF arises from its very high lattice energy which makes crystalline LiF a thermodynamic trap.^[4b]

Recently, we have described the synthesis of trimeric organometallic complexes of the general formula [L_nM(C₅H₃NO₂)]₃ (L_nM = arene-Ru or Cp^{*}Rh; Cp^{*} = C₅Me₅).^[5] These analogues of [12]crown-3^[6] were shown to bind alkali metal halides with remarkable affinity and selectivity. In an extension of this work we have investigated the reaction of [Cp^{*}IrCl₂]₂ with 3-hydroxy-2-pyridone in the presence of base. As in the cases with the analogous ruthenium and rhodium complexes, a trimeric complex [Cp^{*}Ir(C₅H₃NO₂)]₃ (**1**) was obtained. The metallamacrocyclic was characterized by NMR spectroscopy (¹H, ¹³C), elemental analysis, and single-crystal X-ray analysis (Figure 2).^[7] A pseudo-C₃-symmetric geometry is observed in the solid state, with dianionic pyridonate ligands bridging the Cp^{*}Ir^{III} frag-

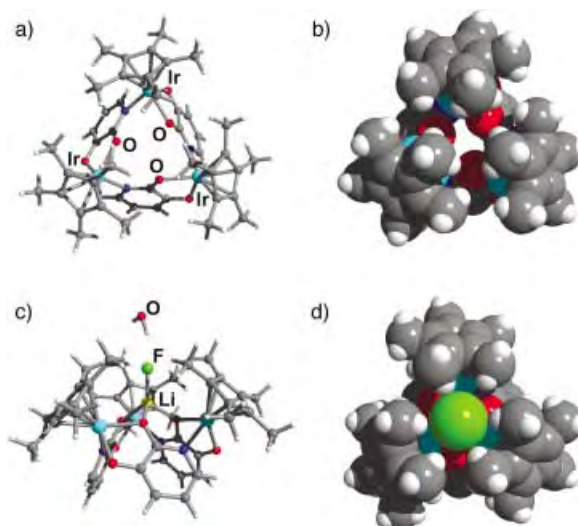


Figure 2. a) The molecular structure of **1** in the crystal; b) view along the pseudo-C₃ axis of **1** highlighting the sterically shielded binding site (space filling representation); c) the molecular structure of **1** · LiF in the crystal; d) view along the pseudo-C₃ axis of **1** · LiF. Four very short CH...F contacts are observed (the water molecule is omitted in the space filling representation).

[*] Prof. K. Severin, M.-L. Lehaire, Dr. R. Scopelliti^[+]
Institut de Chimie Moléculaire et Biologique
École Polytechnique Fédérale de Lausanne, BCH
1015 Lausanne (Switzerland)
Fax: (+41) 21-693-9305
E-mail: kay.severin@epfl.ch
Dr. H. Piotrowski^[+]
Department Chemie
Ludwig-Maximilians Universität München
Butenandtstrasse 5–13, 81377 München (Germany)

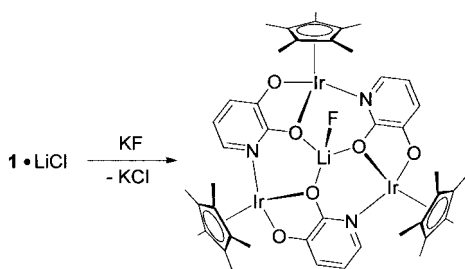
[+] X-ray structural analyses.

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ments. Three oxygen donor atoms are positioned in a cavity that is well shielded by the Cp* ligands.

Although the molecular structure of **1** in the crystal is similar to that of the corresponding rhodium complex [Cp*Rh(C₅H₃NO₂)₃] (**2**),^[5b] the host–guest properties were found to be strikingly different. If **2** is dissolved in CD₃CN saturated with LiCl, the adduct **2**·LiCl is obtained in quantitative yield in less than eight minutes as evidenced by ¹H NMR spectroscopy. For the iridium complex **1**, on the other hand, the complexation of LiCl takes more than one hour. The half-life was determined to be 19 minutes with a pseudo first-order rate constant of $k = 5.8 \times 10^{-4} \text{ s}^{-1}$. Compared to other Li⁺ ionophores, this is a remarkably slow reaction.^[8] The small association rate constant indicated that the binding site of receptor **1** is very rigid and sterically shielded. These characteristics prompted us to investigate the possibility of using **1** for the construction of a fluoride ion sensor as schematically depicted in Figure 1.

First, we have examined whether the metallacrown **1** can be used to stabilize molecular LiF. The molecule has to be prepared in situ because of the very low solubility of LiF. Therefore, we have synthesized the adduct **1**·LiCl, which was subsequently treated with an excess of KF in a mixture of benzene and CH₃OH (140:1). We were able to isolate the complex **1**·LiF in analytically pure form by crystallization from benzene/pentane (Scheme 1).



Scheme 1. Synthesis of **1**·LiF by anion exchange.

The successful Cl–F anion exchange was evident from the NMR spectroscopic data: the ⁷Li NMR spectrum of **1**·LiF shows a doublet resulting from coupling to the adjacent fluoride ion, while the ¹⁹F NMR spectrum displays a quartet resulting from coupling to a ⁷Li center (Figure 3). The ¹⁹F–⁷Li coupling constant of 101 Hz is larger than those found for other compounds with Li···F contacts.^[9]

In the crystal, the LiF complex shows a triangular geometry similar to that of the free receptor **1** (Figure 2).^[7] The presence of the guest molecule results in a slightly expanded macrocycle with an average Ir···Ir distance of 5.43 Å (**1**: 5.37 Å). The lithium ion is coordinated to the three O atoms inside the cavity (Li–O = 1.97, 2.00, and 2.02 Å) with the fourth coordination site being occupied by the fluoride ion. The Li–F distance is of special interest: with 1.755(11) Å it is significantly shorter than that found for crystalline LiF (2.009 Å).^[10] The difference can be attributed, at least partially, to the reduced coordination numbers of the Li⁺ as well as of the F[–] ion. The compound [Li(THF)₂P(SiF₂Bu₂)₂], for example,

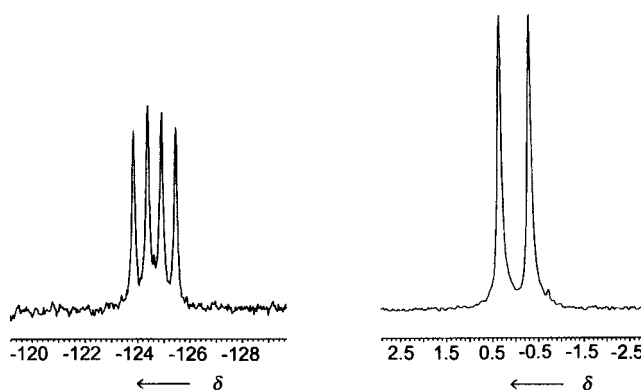


Figure 3. ¹⁹F (left) and ⁷Li NMR (right) spectra of complex **1**·LiF (C₆D₆).

with a fourfold coordinate Li⁺ ion shows a Li–F bond length of 1.843(15) Å.^[11]

The fluoride ion is positioned at the opening of the cavity. As a result, four very short CH···F contacts between the Cp* ligands and the F[–] ion can be observed (CH···F = 2.15–2.28 Å). This very tight encapsulation of the fluoride ion is expected to contribute to the overall stability of the host–guest complex.^[12] Furthermore, the fluoride ion is bound through a hydrogen bond to a water molecule (F···O = 2.640(7) Å).

After having established that the macrocycle **1** is able to complex LiF, we have investigated whether lithium salts of **1** can be employed for the selective recognition of a fluoride anion. For this purpose we have synthesized the adduct **1**·LiBF₄. The X-ray structural analysis revealed that in the solid state the salt is likewise bound as an ion pair with an almost linear Li(μ-F)BF₃ fluoro bridge (172.9(7)°).^[7] The Li–F bond length of 1.957(16) Å is significantly longer than that found for **1**·LiF and that calculated for [(H₂O)₃Li(μ-F)BF₃] (1.768 Å).^[4a] The adduct shows, once again, a pseudo-C₃ molecular symmetry with short CH···F contacts ranging from 2.27 to 2.49 Å. NMR data indicate that in solution (CDCl₃:CD₃CN, 2:1) the weakly bound BF₄[–] ion is not coordinated to the lithium ion: even at low temperatures coupling between ⁷Li and ¹⁹F centers cannot be observed. Furthermore, the ¹H and ⁷Li NMR spectra of **1**·LiCl and **1**·LiBF₄ are identical, which suggests that in both cases the ion-separated, solvated complex [**1**·Li⁺(Solv.)_x] (Solv. = solvent) is present. If 0.5 equivalents of NBu₄F are added to a solution of **1**·LiBF₄, signals of the ion-paired complex **1**·LiF are immediately observed by ¹⁹F and ⁷Li NMR spectroscopy. The clearly distinguishable signals of **1**·LiF appear in the ¹H NMR spectrum. These experiments showed that the cationic complex [**1**·Li⁺(Solv.)_x], generated by dissolving **1**·LiBF₄ in a mixture of CDCl₃ and CD₃CN, acts as a high-affinity receptor for fluoride anions. In contrast to the complexation of the lithium cation by the free receptor **1**, the coordination of the fluoride anion to [**1**·Li⁺(Solv.)_x] is very fast.

To test the selectivity of the receptor we have performed competition experiments with **1**·LiBF₄, NBu₄X (X[–] = Cl[–], Br[–], I[–], NO₃[–]), and NBu₄F·3H₂O (receptor:X[–]:F[–] = 1:100:2). In spite of the large excess of the competing anion (X[–]), the exclusive formation of **1**·LiF was determined by

NMR spectroscopy (^1H , ^7Li) in all cases.^[13] Given that the yield of $\mathbf{1} \cdot \text{LiF}$ is at least 97%, the fluoride/ X^- selectivity must be higher than 1.6×10^3 .^[14]

A receptor with high affinity and selectivity is a prerequisite for potential applications in fluoride sensing. However, the possibility to transduce the binding event into some kind of signal output is likewise of central importance. In this respect, electrochemical responses are especially suited.^[15] When a solution of the complex $\mathbf{1} \cdot \text{LiBF}_4$ in $\text{CHCl}_3:\text{CH}_3\text{CN}$ (2:1) was investigated by differential pulse voltammetry, the peak potential for the first oxidation of the redox-responsive host was observed at 890 (± 3) mV (against Ag/AgCl).^[16] The complex was significantly easier to oxidize ($\Delta E = -203$ mV) when five equivalents of NBu_4F were added, presumably because the electron-withdrawing character of the ion-paired LiF guest is smaller than that of the solvated lithium ion (Table 1). In agreement with the NMR studies, only small changes were observed upon addition of Cl^- , Br^- , NO_3^- , HSO_4^- , or ClO_4^- salts ($\Delta E < 24$ mV). Similar results were obtained in solutions containing methanol ($\text{CDCl}_3:\text{CD}_3\text{CN}:\text{CH}_3\text{OH} = 4:2:1$). This result is in contrast to many other fluoride receptors which cannot be used in protic solvents.^[1, 2] It should be pointed out that all electrochemical investigations were carried out in 0.1 M NBu_4BF_4 as a supporting electrolyte. Apparently, the very large excess of BF_4^- ions ($\text{BF}_4^-:\text{F}^- = 140:1$) does not interfere with the selective detection of fluoride ions.

Table 1. Absolute difference of the peak potential for the first oxidation of $\mathbf{1} \cdot \text{LiBF}_4$ (0.36 mM) after addition of five equivalents of NBu_4X .^[a]

X^-	ΔE [mV] solvent A	ΔE [mV] solvent B
F^-	203	191
Cl^-	24	< 20 ^[b]
Br^-	6	< 20 ^[b]
NO_3^-	24	18
HSO_4^-	12	0
ClO_4^-	6	0

[a] Determined by differential pulse voltammetry. Solvent A: $\text{CHCl}_3:\text{CH}_3\text{CN}$ (2:1); solvent B: $\text{CHCl}_3:\text{CH}_3\text{CN}:\text{CH}_3\text{OH}$ (4:2:1). [b] The peak appears as a shoulder.

In summary, we have shown that the organometallic metallacrown complex $\mathbf{1}$ can act as a receptor for LiF . To the best of our knowledge, the resulting adduct $\mathbf{1} \cdot \text{LiF}$ represents the first structurally characterized complex of molecular LiF . The unique situation of LiF inside the macrocyclic host is reflected by the very short $\text{Li} \cdots \text{F}$ distance and the large ^{19}F - ^7Li NMR coupling constant, unparalleled by other compounds with $\text{Li} \cdots \text{F}$ contacts. On the basis of these results, we have constructed a highly selective chemosensor that allows the detection of fluoride anions by electrochemical means, even in protic solvents.

Received: December 19, 2001 [Z18415]

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anisotropically defined. H atoms were placed in calculated positions using the riding model. CCDC-175844 (**1**), CCDC-175845 (**1**·LiF), and CCDC-175846 (**1**·LiBF₄) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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).

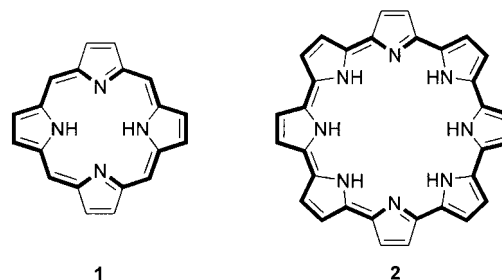
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Cyclo[8]pyrrole: A Simple-to-Make Expanded Porphyrin with No Meso Bridges**

Daniel Seidel, Vincent Lynch, and Jonathan L. Sessler*

*Dedicated to Professor James P. Collman
on the occasion of his 70th birthday*

Porphyrin (for example, **1**), a tetrapyrrolic macrocycle, is the active component of many naturally occurring pigments and has been known and studied for centuries; its biological importance can hardly be overestimated.^[1] In spite of this ubiquity, it was only in 1966 that the first expanded porphyrin analogue, sapphyrin, was reported,^[2] and it has only been in recent years that the area of expanded porphyrin research has begun to attract attention as its own rapidly evolving field.^[3–5] One of the unexpected surprises to emerge from this work is the finding that large expanded porphyrins (those containing eight or more pyrrole rings) are often not flat but rather adopt “figure-eight” and other twisted conformations in spite of being highly conjugated.^[6–11] It thus remains a challenge at present to produce large aromatic expanded porphyrins that display the classic disklike structure of simple porphyrins.^[12–15]



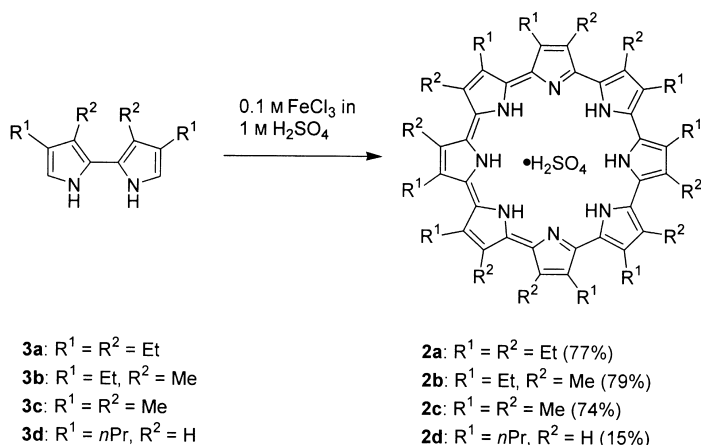
One structure that might allow this elusive goal to be met is cyclo[8]pyrrole (**2**; [30]octaphyrin(0.0.0.0.0.0.0)). This target can be derived, at least in theory, by replacing all four meso-carbon bridges with four additional pyrrolic rings. If it is produced in this way, cyclo[8]pyrrole would possess an extended 30- π -electron periphery that, in analogy to the 18- π -electron system of porphyrin, would be aromatic in a Hückel ($4n+2$) π -electron sense (compare **1** and **2**).

A retrosynthetic analysis of **2** leads to the consideration that it could be “split up” by disconnection of one or more of the α - α' bonds between the individual pyrrolic subunits, which means it could be prepared (at least in principle) from linear oligopyrrolic fragments, such as a linear octipyrrolic unit, two quaterpyrrolic units, four bipyrrolic units, or ultimately eight

[*] Prof. Dr. J. L. Sessler, D. Seidel, Dr. V. Lynch
Department of Chemistry and Biochemistry
and Institute for Cellular and Molecular Biology
University of Texas at Austin
Austin, TX 78712-1167 (USA)
Fax: (+1) 512-471-7550
E-mail: Sessler@mail.utexas.edu

[**] This work was supported by the National Science Foundation (grant CHE 0107732 to J.L.S.). The authors would like to thank Dr. Paul Fleitz and Weijie Su (Wright Patterson Air Force Base) for recording the UV/Vis spectrum of **2b**.

pyrrolic units. To date, however, the preparation of higher order fused oligopyrrolic systems, including α,α' -unsubstituted quaterpyrroles, has proved elusive.^[16–18] Therefore, we decided to concentrate our efforts on a simple one-pot strategy that would involve the direct coupling of bipyrrolic fragments (Scheme 1). Accordingly, several readily available substituted and unsubstituted bipyrroles were subjected to a wide range of potential coupling conditions, such as ones involving condensation of the bipyrrole with SCl_2 and subsequent sulfur extrusion of the putative thia-bridged macrocyclic intermediates^[19] as well as various oxidative coupling procedures.^[13–15, 17, 18, 20–29] Among the latter were the Cr^{VI} -based oxidative coupling method described by Falk and Flödl,^[23] which we have recently found useful in the synthesis of other expanded porphyrins,^[17, 18] and strategies based on the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranil—reagents that have been used to prepare a range of expanded^[13–15, 20–22] and contracted porphyrins.^[25–29] Finally, success was encountered using FeCl_3 as the oxidant. Ferric chloride has been used frequently in the synthesis of polypyrroles,^[30] but has not, at least to the best of our knowledge, ever been used to produce expanded porphyrin-type coupling products. It has, however, been employed to aromatize macrocycles.^[31, 32] Herein, we report a highly efficient one-step synthesis of cyclo[8]pyrroles (**2**) that is based on the use of FeCl_3 as the oxidant and readily accessible α,α' -unsubstituted bipyrroles^[33–35] as the only organic precursors (Scheme 1).



Scheme 1. Direct coupling of bipyrrolic fragments to form cyclo[8]pyrroles.

While the FeCl_3 -induced oxidative coupling of bipyrroles produces cyclo[8]pyrroles of general structure **2** under a range of conditions, we have found that the best yields are obtained under carefully optimized biphasic conditions (bipyrrole in CH_2Cl_2 , FeCl_3 in 1 M H_2SO_4).^[36] In this optimized procedure the rate of addition is carefully controlled so as to ensure a very low concentration of bipyrrole in the organic phase at all times. Also, the stirring speed is kept low, so as to minimize the extent to which the two phases are allowed to mix.^[37]

The yields of cyclo[8]pyrroles, isolated under these conditions in the form of their dihydrogen sulfate salts, are remarkably good, being above 70 % in the case of **2a–c**

(Scheme 1). Such yields are noteworthy in the area of expanded porphyrin chemistry and rival the best yields seen in the synthesis of β -substituted octaalkylporphyrins.^[38] On the other hand, the yields observed for **2d** are significantly lower (15 %). While a variety of factors could account for this finding, it is currently rationalized in terms of the lack of full β -substitution which would allow competing β – β' or β – α coupling reactions to occur. Consistent with this proposal is the finding that simple unsubstituted bipyrrole does not give rise to isolable quantities of cyclo[8]pyrrole, even when subjected to FeCl_3 -based oxidation under the optimized conditions.^[39]

The NMR spectra of the cyclo[8]pyrrole dihydrogen sulfate salts **2a–d** are characterized by their unusually high symmetry. Compounds **2a–d** are judged to be aromatic on the basis of the positions of the signals observed in their respective ^1H NMR spectra. Specifically, the signal corresponding to the NH protons in the spectrum of **2a** recorded in CDCl_3 at room temperature appears at $\delta = 0.64$, clearly upfield from “normal” pyrrolic NH protons. The only two remaining signals, a triplet at $\delta = 1.63$ and an unresolved quartet at $\delta = 4.17$, are assigned to the single, chemically distinct (that is, magnetically degenerate) ethyl group. While unresolved at room temperature, the quartet at $\delta = 4.17$ corresponding to the CH_2CH_3 protons displays a chemical shift that is typical for a methylene group attached directly to the periphery of an aromatic expanded porphyrin-type macrocycle.^[17] This CH_2CH_3 signal is nearly resolved as a distinct quartet at low temperature (223 K, CDCl_3), while the NH resonance shifts to $\delta = -0.2$.

The ^1H NMR spectra of cyclo[8]pyrroles **2b–d** are similar to that of **2a**. However, in addition to the expected differences in the alkyl region (and the observation of a β -CH signal at $\delta = 9.9$ in the case of **2d**) a noticeable trend in the position of the NH resonances is observed. Specifically, the NH signal for **2b** at room temperature in CDCl_3 is seen at $\delta = -0.64$, while the corresponding signals for **2c** and **2d** are observed at $\delta = -0.84$ and -1.63 , respectively. These differences are interpreted in terms of the latter, less sterically hindered systems being better able to adopt conformations that lie closer to true planarity.

Also underscoring the high symmetry of **2a–d**, and hence their inferred near-planarity, are their respective ^{13}C NMR spectra. Here, the prototypic spectrum is that of **2c**, which displays only three distinct signals. Such a limited number of signals is quite unusual for a molecule with 48 carbon atoms and a molecular weight of 841 Da. If perturbations that arise from the sulfate counterion are excluded, **2c** is left with an effective D_{8h} symmetry in solution.

The results of a single-crystal X-ray diffraction analysis of **2b** are consistent with the proposal that cyclo[8]pyrroles **2** are flat or nearly flat.^[40] The resulting structure (Figure 1) reveals a very flat, essentially planar macrocyclic system with a sulfate ion centrally bound within the cavity. Eight hydrogen-bonding interactions are inferred in the solid state from the $\text{NH}\cdots\text{O}$ distances which range from 1.91 to 2.49 Å. The result is a structure wherein all four oxygen atoms of the sulfate counterion interact with all eight pyrrole NH sites present in the middle of what is formally a diprotonated receptor. While

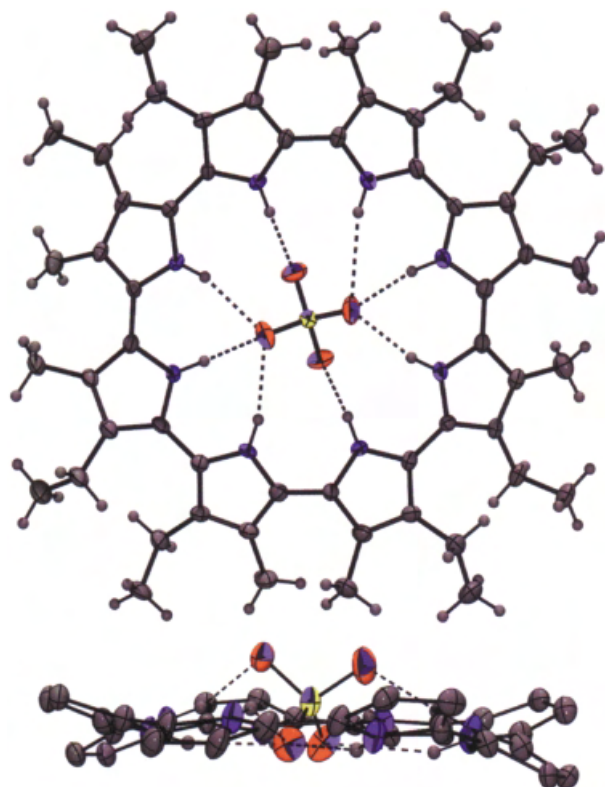


Figure 1. Ortep-POV-Ray views of one of the two crystallographically independent molecules seen in the solid-state structure of **2b**. The thermal ellipsoids are scaled to the 50% probability level.

not a proof, this finding, which has antecedents in the expanded porphyrin literature,^[3, 5, 18, 41] leads to the suggestion that cyclo[8]pyrroles such as **2a–d** could emerge as useful anion receptors.

The UV/Vis spectrum of **2b** (Figure 2) is characterized by a relatively weak Soret-type absorbance at 431 nm ($\epsilon = 79800 \text{ mol}^{-1} \text{ cm}^{-1}$) and an intense, red-shifted Q-type band at 1112 nm ($\epsilon = 132200 \text{ mol}^{-1} \text{ cm}^{-1}$). Both the intensity and the position of the latter band are remarkable given that Q-type absorption bands in porphyrinoids (and aromatic expanded systems) are generally far less intense than the corresponding Soret transitions and are rarely as far red-shifted as seen in the present case. Indeed, we are aware of only three other expanded porphyrin systems, namely the doubly cationic hexathiarubyrin of Vogel and co-workers^[7, 42]

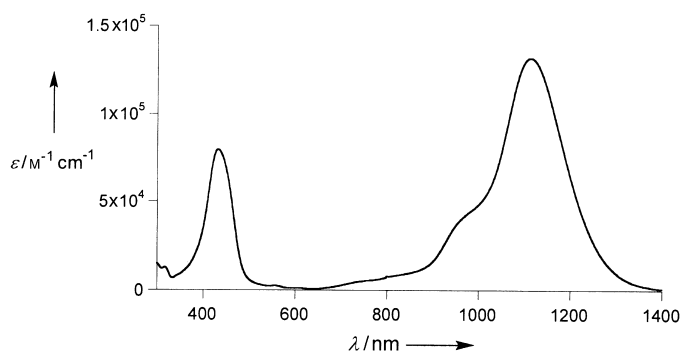


Figure 2. UV/Vis spectrum of **2b** recorded in dichloromethane.

and the recently described octaphyrin(1.1.1.1.1.1.1.1) and nonaphyrin(1.1.1.1.1.1.1.1.1) of Furuta and co-workers^[11] that display Q-type bands at or above 1000 nm. These systems display nowhere near the intensity of **2b**.

In summary, a new biphasic oxidative coupling procedure has been introduced that allows the efficient synthesis of the hitherto unknown cyclo[8]pyrroles. These systems display features that are consistent with Hückel-type $4n+2$ aromaticity. Furthermore, as they are large, flat macrocycles with an “NH-in” arrangement of the pyrrolic nitrogen atoms, they can be considered as new “true” porphyrin analogues.^[43, 44] Currently, we are exploring the extent to which the present coupling procedure can be generalized while working to define further the basic chemistry of cyclo[8]pyrroles.^[45] In preliminary work, we have found that washing a solution of **2b** with 1M aqueous NaOH produces spectral changes that are consistent with the formation of the free base (λ_{max} (ϵ in $\text{mol}^{-1} \text{ cm}^{-1}$) 349 (36200), 455 (15700), and 857 (26900) nm). Treating this species with 1M H_2SO_4 served to restore completely the spectral features of **2b**. Likewise, treatment with 1M H_3PO_4 led to formation of a species tentatively formulated as the corresponding hydrogen phosphate complex. On the other hand, it was found that the sulfate anion observed in the solid-state structure of **2b** is retained after washing a solution of this dihydrogen sulfate salt in dichloromethane with water (pH 7; $3 \times$). These findings taken together lead us to propose that cyclo[8]pyrroles could emerge as interesting anion receptors. A range of other applications, including uses as optical storage and signaling devices based on their unusually strong red-shifted Q-like absorption, can also be envisioned.

Experimental Section

General: ^1H and ^{13}C NMR spectra were measured at 25°C on a Varian Unity Plus spectrometer at 300 MHz or on a Varian Unity Innova at 500 MHz. UV/Vis spectra were recorded at Wright Patterson Air Force Base on a Carey 500 spectrophotometer. High-resolution chemical ionization (CI) mass spectra were obtained on a VGZAB2-E mass spectrometer. A Sage syringe pump (model M365) was employed for slow continuous additions. All solvents and chemicals were obtained commercially and used as received. The bipyrrolic precursors were prepared as described previously.^[33–35]

General Procedure for the oxidative coupling of bipyrroles: A 1-L round-bottom flask was charged with a stir bar, dichloromethane (500 mL), and a solution of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (2.7 g, 10 mmol) in 1M sulfuric acid (100 mL). The resulting biphasic mixture was stirred at 300 rpm, while a solution of the bipyrrole (1 mmol) in dichloromethane (50 mL) was added slowly by syringe pump over a period of 9 h, with the needle submerged into the organic phase. After completion of the addition, the reaction mixture was stirred for 5 h. Subsequently, the phases were separated and the organic phase was dried over anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo to yield the crude product. The crude products were purified by column chromatography on silica gel using dichloromethane containing methanol (2–5%) as the eluent. The yellow band was collected and the solvent removed in vacuo. The solid residue was recrystallized from dichloromethane/methanol to yield **2a–d** as dark microcrystalline powders.

2a: 77% yield; ^1H NMR (500 MHz, CDCl_3): $\delta = 0.64$ (s, 8H, NH), 1.63 (t, $J_{\text{HH}} = 7.5$ Hz, 48H, CH_2CH_3), 4.17 (brs, 32H, CH_2CH_3); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 16.13$, 21.92, 126.26, 128.43; HR-MS (CI): m/z 1065.6710 [$M+\text{H}^+$], calcd for $\text{C}_{64}\text{H}_{89}\text{N}_8\text{O}_4\text{S}_1$: 1065.6727.

2b: 79% yield; ^1H NMR (300 MHz, CDCl_3): $\delta = -0.64$ (s, 8H, NH), 2.07 (t, $J_{\text{HH}} = 7.5$ Hz, 24H, CH_2CH_3), 3.76 (s, 24H, CH_3), 4.17 (q, $J_{\text{HH}} = 7.5$ Hz, 16H, CH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 15.90, 15.99, 22.17, 123.87, 125.34, 126.44, 129.27$; HR-MS (CI): m/z 952.5399 [M^+], calcd for $\text{C}_{36}\text{H}_{72}\text{N}_8\text{O}_4\text{S}_1$: 952.5397; UV/Vis (CH_2Cl_2) λ_{max} [nm] (ϵ in $\text{mol}^{-1}\text{L}^{-1}$): 431 (79800), 1112 (132200).

2c: 74% yield; ^1H NMR (300 MHz, CDCl_3): $\delta = -0.84$ (s, 8H, NH), 3.58 (s, 48H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 15.63, 123.89, 125.87$; HR-MS (CI): m/z 841.4214 [$M+\text{H}^+$], calcd for $\text{C}_{48}\text{H}_{57}\text{N}_8\text{O}_4\text{S}_1$: 841.4224.

2d: 15% yield; ^1H NMR (300 MHz, CDCl_3): $\delta = -1.63$ (s, 8H, NH), 1.31 (t, $J_{\text{HH}} = 7.3$ Hz, 24H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.50–2.63 (m, 16H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.78 (t, $J_{\text{HH}} = 7.9$ Hz, 16H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 9.89 (d, $J_{\text{HH}} = 2$ Hz, 8H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.74, 25.42, 33.34, 114.53, 124.80, 128.10, 133.48$; HR-MS (CI): m/z 953.5461 [$M+\text{H}^+$], calcd for $\text{C}_{56}\text{H}_{73}\text{N}_8\text{O}_4\text{S}_1$: 953.5476.

Received: December 20, 2001 [Z18418]

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- [37] While the yield for cyclo[8]pyrrole formation goes down at higher stirring speeds or faster addition rates, the yield of a blue product (which is not observed under the reaction conditions outlined in the experimental section of this paper) increases. This blue product is tentatively assigned on the basis of a MALDI mass spectrometric analysis to be a cyclo[12]pyrrole. Unfortunately, this product begins to precipitate shortly after elution from the column and is poorly soluble in common organic solvents. This has so far precluded its full characterization.
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- [40] Crystallographic data for **2b**: Dark plates were grown by vapor diffusion of dichloromethane and methanol, triclinic, space group $P\bar{1}$ (No. 2), $Z = 2$, $a = 11.4267(1)$, $b = 21.9142(2)$, $c = 24.5622(3)$ Å, $\alpha = 76.330(1)^\circ$, $\beta = 76.946(1)^\circ$, $\gamma = 81.367(1)^\circ$, $V = 5791.40(10)$ Å³, $\rho_{\text{calcd}} = 1.28$ g cm⁻³, $F(000) = 2396$, $\mu = 0.207$ mm⁻¹. A total of 40398 reflections were measured, 25843 unique ($R_{\text{int}} = 0.045$), on a Nonus Kappa CCD using graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å) at -120°C . The structure was refined on F^2 to $R_w = 0.184$, with a conventional $R = 0.0957$ (13724 reflections with $F_o > 4\sigma(F_o)$), and a GOF = 2.13 for 1311 refined parameters. There are two crystallographically independent macrocycle sulfate complexes. CCDC-176189 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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C–C Coupling between an η^3 -Allyl Ligand and Carbon Nucleophiles in Molybdenum and Tungsten Complexes: Structural Characterization of the Key Intermediate**

Julio Pérez,* Víctor Riera, Amor Rodríguez, and Santiago García-Granda

The Mo-catalyzed allylic alkylation was first reported by Trost and Lautens in 1982^[1] and has been developed into a useful tool in organic synthesis.^[2] It is accepted that in this reaction the oxidative addition of the allylic electrophile to a low-valent molybdenum carbonyl complex gives a η^3 -allyl complex, which subsequently undergoes attack by the nucleophile.^[3] Accordingly, $[\text{MoCl}(\eta^3\text{-allyl})(\text{CO})_2(\text{L-L})]$ ($\text{L-L} = 2,2'$ -bipyridine (bpy) or 1,2-bis(diphenylphosphanyl)ethane (dppe)) complexes react with stabilized carbanions to afford olefins.^[1, 4] Despite studies on this reaction^[3] and the related W-catalyzed allylic alkylation,^[5] some important mechanistic questions remain open. Thus, as stated in the seminal paper by Trost and Lautens,^[1] nucleophilic attack can take place either directly at the allyl group or primarily at the metal center, followed by a metal-to-allyl migration of the alkyl group.

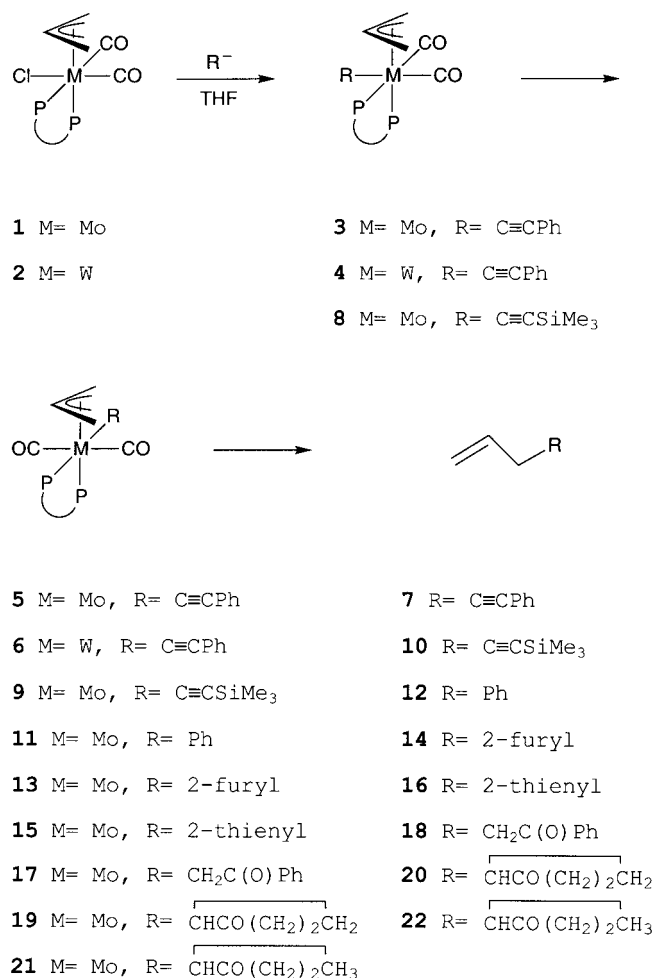
We recently found that $[\text{MoCl}(\eta^3\text{-allyl})(\text{CO})_2(\text{N-N})]$ complexes react with nonstabilized alkyl nucleophiles to yield $[\text{Mo}(\text{R})(\eta^3\text{-allyl})(\text{CO})_2(\text{N-N})]$ alkyl complexes.^[6] In these complexes, whose geometry is reminiscent of that of the chloro precursors,^[7] the alkyl and allyl groups are in mutually *trans* positions and, as a result, alkyl migration to the allyl ligand was not observed.

$[\text{MoCl}(\eta^3\text{-allyl})(\text{CO})_2(\text{P-P})]$ diphosphane complexes have a different structure, in which the Cl and allyl ligands are in *cis* positions.^[8] We reasoned that substitution of Cl^- by R^- with retention of the geometry in these diphosphane complexes, as in the diimine counterparts, would afford products in which coupling between the adjacent R and allyl groups could be viable. To begin our study, we chose acetylide anions because alkynyl complexes are more stable than their alkyl counterparts.^[9]

Preliminary experiments with bis(diphenylphosphanyl)methane (dppm) and dppe complexes afforded products from which we were unable to isolate pure samples, whereas the related $[\text{MCl}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2(\text{dmpm})]$ ($\text{M} = \text{Mo}$ (**1**), W (**2**), $\text{dmpm} = (\text{dimethylphosphanyl})$) compounds led to more trac-

table products and the reactivity of these complexes is described herein.

The reactions of **1** and **2** with lithium phenylacetylide gave metal species with two similarly intense ν_{CO} bands at wavenumbers lower than for **1** and **2**, as expected for the substitution of Cl for $\text{C}\equiv\text{CPh}$. These compounds (**3** and **4**), for which the *cis* geometry depicted in Scheme 1 can be



Scheme 1. Reactions of **1** and **2** with acetylide, alkyl, and enolate carbanions.

assumed, could not be further characterized because of their rapid transformation into the new complexes **5** and **6**, respectively, which displayed single ν_{CO} IR bands. These complexes decomposed in solution; however, in the case of **6** this decomposition was slow enough to permit a full characterization (see Experimental Section) in solution and the crystallization and subsequent structural determination by X-ray diffraction (Figure 1).^[10]

Compound **6** comprises a tungsten atom coordinated to a chelating dmpm ligand, a η^3 -allyl group, a phenylalkynyl ligand, and two carbonyl groups. The CO ligands are in mutually *trans* positions,^[12] an arrangement that is considered to be electronically disfavored, and unprecedented for pseudooctahedral allylmolybdenum dicarbonyl complexes.^[7]

The solutions obtained from the decomposition of complexes **5** and **6** (disappearance of ν_{CO} IR bands, and the

[*] Dr. J. Pérez, Prof. Dr. V. Riera, A. Rodríguez
Departamento de Química Orgánica e Inorgánica/I.U.Q.O.E.M.
Facultad de Química
Universidad de Oviedo-C.S.I.C., 33071 Oviedo (Spain)
Fax: (+34)98-510-3446
E-mail: japm@sauron.quimica.uniovi.es

Dr. S. García-Granda
Departamento de Química Física y Analítica
Facultad de Química
Universidad de Oviedo, 33071 Oviedo (Spain)

[**] This work was supported by the Ministerio de Ciencia y Tecnología (grants BQU2000-0220 and BQU2000-0219) and the FICYT (grants PR-01-GE-7 and PR-01-GE-4).

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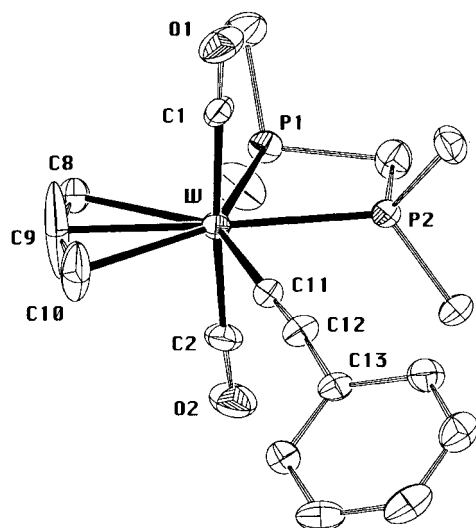


Figure 1. Structure of **6** (thermal ellipsoid plot (30% probability)). Selected bond lengths [Å] and angles [°]: W-C11 2.177(9), C11-C12 1.192(11), C12-C13 1.430(11); C1-W-C2 175.2(3), C11-C12-C13 172.6(9).

observation of a large number of ^{31}P MNR signals in the resulting solution showed the decomposition of the metal complex to several unidentified species) contained the non-conjugate enyne 1-phenyl-4-penten-1-yne (**7**), which resulted from the coupling between the alkynyl group and a terminal carbon atom of the allyl group. Monitoring of the reaction by ^1H NMR spectroscopy in CD_2Cl_2 revealed quantitative formation of the enyne from **5** and **6**. Since η^3 -allyl complexes^[13] are normally the target of nucleophilic attack, and alkynyl groups typically react with electrophiles, enyne formation can be presumed to occur by an alkynyl-to-allyl intramolecular migration.^[14] Analogous results were obtained by employing lithium trimethylsilylacetylide (see Scheme 1; **9**–**10**).

The reaction of the **1** with phenyl- (via **11** to give **12**), 2-furyl- (via **13** to give **14**), and 2-thienyllithium reagents (via **15** to give **16**) followed a similar path. Only the *trans*-dicarbonyl complexes were detected by IR spectroscopy, probably as a result of a fast *cis*-to-*trans* isomerization. Decomposition of the metal complexes afforded the olefins resulting from alkyl-allyl coupling (Scheme 1). Similar results were obtained with the enolates of acetophenone, cyclopentanone, and cyclohexanone, which afforded the C–C coupled products **18**, **20**, and **22**, respectively (see Scheme 1).

These results demonstrate that acetylide, alkyl, and enolate carbanions attack at the metal center in $[\text{MCl}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2(\text{dmpm})]$ ($\text{M} = \text{Mo}$ (**1**), W (**2**)) complexes, leading to a stereospecific substitution of the chloro ligand by the incoming nucleophile. The products then undergo a *cis*-to-*trans* isomerization, which is unprecedented for this kind of complexes, and, subsequently, the spontaneous elimination of the alkynyl-allyl, alkyl-allyl, or enolate-allyl product. Nucleophilic attack at the metal center followed by a metal-to-allyl migration, which was proposed as a possible mechanistic path two decades ago for pseudooctahedral allyl-molybdenum complexes,^[1] has been, therefore, experimentally substantiated for the first time.

Experimental Section

All operations were carried out under an atmosphere of dry dinitrogen by using Schlenk techniques. Solvents were dried over Na (hexane) and CaH_2 (CH_2Cl_2 and MeOH) and distilled immediately prior to use. IR spectra were recorded in solution in THF. Correct elemental analyses were obtained for the new complexes.

1: The addition of dmpm (50 μL , 0.32 mmol) to $[\text{MoCl}(\eta^3\text{-C}_3\text{H}_5)(\text{CO})_2(\text{NCMe})_2]$ ^[15] (0.10 g, 0.32 mmol) in CH_2Cl_2 (10 mL) gave a red solution which was stirred for 5 min. The volume of this solution was reduced under vacuum to one third, and hexane was added to precipitate **1** as an orange crystalline solid. Yield: 0.11 g, 94%; IR: $\tilde{\nu} = 1944\text{s}$, 1845s cm^{-1} ; $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta = -24.38$; ^1H NMR (CD_2Cl_2): $\delta = 4.75$ (m, 1 H; Hc), 3.69 (m, 2 H; *syn*-H), 3.24 (m, 2 H; CH_2 (dmpm)), 2.31 (d, $^3J(\text{H,H}) = 12$ Hz, 2 H; *anti*-H), 1.73 (apparent triplet (at), $^2J(\text{P,H}) = 5$ Hz, 6 H; CH_3 (dmpm)), 1.65 (at, $^2J(\text{P,H}) = 5$ Hz, 6 H; CH_3 (dmpm)); $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2): 226.68 (at, $^2J(\text{P,C}) = 8$ Hz; CO), 98.68 (s; C_2 allyl), 62.36 (s; C1 and C3 (allyl)), 40.65 (at, $^1J(\text{P,C}) = 23$ Hz; CH_2 (dmpm)), 17.34 (at, $^1J(\text{P,C}) = 14$ Hz; CH_3 (dmpm)), 13.40 (at, $^1J(\text{P,C}) = 13$ Hz; CH_3 (dmpm)).

5: $\text{LiC}\equiv\text{CPh}$ (0.27 mmol in THF (5 mL)) was added to a solution of **1** (0.10 g, 0.27 mmol) in THF (20 mL) at -78°C . The red color darkened immediately and the IR spectrum showed bands at 2072 w, 1935 s, and 1820s cm^{-1} , which were assigned to **3**. After stirring (40 min, RT, trans-formation to **5** was monitored by IR spectroscopy), solvent evaporation, extraction (CH_2Cl_2 , 5 mL), filtration (alumina, grade IV), and evaporation, **5** was obtained. Yield: 0.09 g, 68.1%; IR: $\tilde{\nu} = 2074\text{w}$, 1852s cm^{-1} ; $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2): $\delta = -8.85$, -20.04 (ABq, $^2J(\text{P,P}) = 81$ Hz); ^1H NMR (CD_2Cl_2): $\delta = 7.28$ – 7.15 (m, 5 H; Ph), 5.25 (m, 1 H; Hc), 3.19 (m, 2 H; CH_2 (dmpm)), 3.05 (m, 2 H; *syn*-H); 2.93 (d, $^3J(\text{H,H}) = 9$ Hz, 1 H; *anti*-H), 2.06 (dd, $^3J(\text{H,H}) = 11$ Hz, $^3J(\text{H,H}) = 3$ Hz, 1 H; *anti*-H), 1.93 (d, $^2J(\text{P,H}) = 10$ Hz, 3 H; CH_3 (dmpm)), 1.74 (at, $^2J(\text{P,H}) = 10$ Hz, 3 H; CH_3 (dmpm)), 1.70 (d, $^2J(\text{P,H}) = 9$ Hz, 3 H; CH_3 (dmpm)), 1.53 (d, $^2J(\text{P,H}) = 9$ Hz, 3 H; CH_3 (dmpm)). Compound **5** decomposed in solution in 2 h to give a quantitative (^1H NMR) amount of 1-phenyl-4-penten-1-yne (**7**).^[14]

11, **13**, **15**, **18**, **20**, **22:** PhLi (0.13 mL of a 1.8 M solution, 0.23 mmol) was added to a solution of **1** (0.10 g, 0.23 mmol) in THF (20 mL). After 10 min, the IR spectrum showed a single ν_{CO} band at 1841 cm^{-1} , which was assigned to **11**. After 2 h at room temperature, a procedure analogous to that for **5** afforded allylbenzene (**12**).

Similar reactions were conducted with Li (alkyl) or K (enolate) reagents to give the products indicated in Scheme 1. Available data for the *trans*-dicarbonyl complexes, reaction times, and references for the non-commercial coupling products are given: **11:** IR: $\tilde{\nu} = 1841\text{s cm}^{-1}$, 2 h; **12:** commercial; **13:** $\tilde{\nu} = 1840\text{s cm}^{-1}$, $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = -4.72$, -18.79 (ABq, $^2J(\text{P,P}) = 69.5$ Hz), 30 min; **14:**^[16]; **15:** $\tilde{\nu} = 1845\text{s cm}^{-1}$, 40 min; **16:**^[17]; **17:** $\tilde{\nu} = 1840\text{s}$, 1689s cm^{-1} , $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): $\delta = 67.27$, 11.73 (ABq, $^2J(\text{P,P}) = 26.8$ Hz), 2 h; **18:**^[18]; **19:** $\tilde{\nu} = 1847\text{s}$, 1784s cm^{-1} , 4 h; **20:**^[19]; **21:** $\tilde{\nu} = 1843\text{s}$, 1785s cm^{-1} , 4 h; **22:** commercial. Experimental details for **2**, **6**, and **9** are in the Supporting Information.

Received: February 4, 2002 [Z18650]

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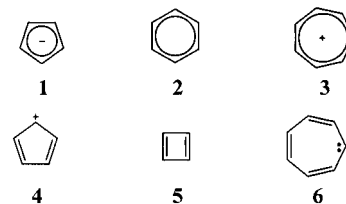
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The Stable Pentamethylcyclopentadienyl Cation**

Joseph B. Lambert,* Lijun Lin, and Vitaly Rassolov

The cyclopentadienyl anion, C_5H_5^- (**1**, Cp^-), was first prepared one hundred years ago.^[1] In due course it became a classic example of aromaticity, exemplifying the Hückel $4n+2$

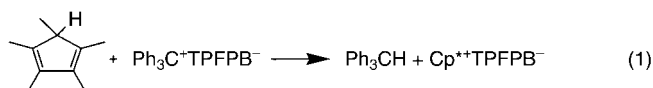
rule for π electrons, along with benzene (**2**) and the tropylium cation (**3**).^[2-4] In contrast, the cyclopentadienyl cation, C_5H_5^+ (**4**, Cp^+) has languished experimentally as an elusive charge



variant. It shares with cyclobutadiene^[5-7] (**5**) and the cycloheptatrienyl anion^[8] (**6**), among others, the characteristics of possessing $4n$ π electrons and thus potentially being antiaromatic.

No simple cyclopentadienyl cation has been structurally characterized. Several studies have reported electron spin resonance (ESR) spectra,^[9] and some studies have implied the species as an intermediate.^[10] These investigations variously looked at the pentachloro, pentaphenyl, and pentamethyl derivatives as well as the unsubstituted molecule. In general, the observed cations were relatively unstable, possessed triplet multiplicity, and needed protective environment.

We now report the preparation of the pentamethylcyclopentadienyl cation C_5Me_5^+ (Cp^{*+}) as the tetrakis(pentafluorophenyl)borate (TPFPB^-) salt. The crystalline material obtained is stable for weeks at room temperature and can be left exposed to the open atmosphere without serious decomposition. We have solved the X-ray structure and obtained NMR spectra in the solid state and in solution. This material may be obtained in one step at room temperature by hydride abstraction from commercially available pentamethylcyclopentadiene [Eq. (1)].^[11, 12] The trityl cation (Ph_3C^+ , with the



anion TPFPB^-) is converted into triphenylmethane, whereas pentamethylcyclopentadiene is converted into the corresponding cation. Crystals of the product began forming immediately and spontaneously. The overall yield is nearly quantitative, and yields of crystals have reached 40%. The reaction has been carried out in several solvents (benzene, toluene, dichloromethane) and with alternative (silyl) leaving groups.

The remarkable stability of this material may be attributed to a number of factors. First, the methyl groups clearly are critical, as analogous experiments with the unsubstituted system were unsuccessful. The methyl group serves as an electron donor and also may play a steric role, as described subsequently. The second key factor is the choice of the counteranion. Many anions of low nucleophilicity now are available.^[13] We previously utilized TPFPB^- in the preparation of the first silylium cation^[14] and employ this same anion in the present study. Finally, choice of solvent also is critical, as

[*] Prof. J. B. Lambert, L. Lin
Department of Chemistry
Northwestern University
Evanston, IL 60208-3113 (USA)
Fax: (+1) 847-491-7713
E-mail: jlambert@northwestern.edu
Prof. V. Rassolov
Department of Chemistry
University of South Carolina
Columbia, SC 29208 (USA)

[**] This work was supported by the U.S. National Science Foundation (Grant No. CHE-0091162). We thank Charlotte L. Stern for performing the crystal-structure analysis, Yuyang Wu for assistance in obtaining solid-state NMR data, Min Zhao and Stoyan Smoukov for providing ESR data, Alice L. Rodriguez for molecular modeling graphics, and John A. Pople and Mark A. Ratner for important discussions.

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solvents with higher nucleophilicity than those of arenes or halocarbons react with the cation.

The crystal structure^[15] of the cation with its anion is depicted in Figure 1. As the edge view (Figure 2a) shows, the molecule is modestly nonplanar (the five internal ring dihedral angles are 4.1(6), 6.6(6), 4.6(5), 6.9(6), and 0.5(5)°). Three carbon atoms (C1, C2, C3) and their attached methyl groups form a nearly planar substructure closely resembling a 1,2,3-trimethylallyl group. Atoms C4 and C5, respectively, are below and above this plane, and their attached methyl groups protrude appreciably from the plane, the CH₃-C4-C5-CH₃ dihedral angle being 106.9(6)°.

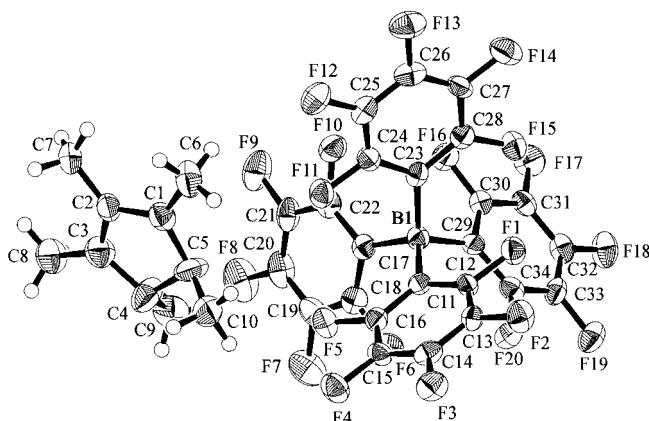


Figure 1. The crystal structure of pentamethylcyclopentadienyl tetrakis(pentafluorophenyl)borate. There is no covalent bonding between the cation on the left and the anion on the right.

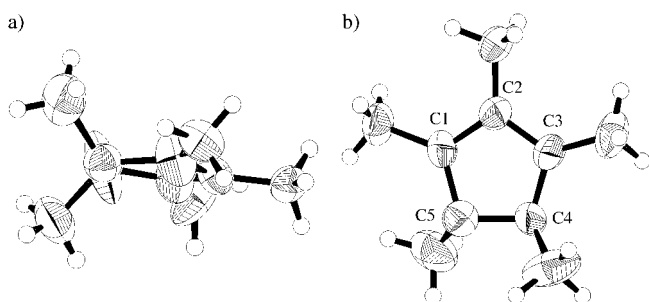
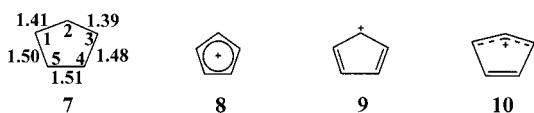


Figure 2. a) Edge view of the pentamethylcyclopentadienyl cation, sighted down the C4-C5 bond on the left. The nearly planar allyl portion is on the right. b) Top view.

The view from the top (Figure 2b) shows an irregular pentagon. The irregularity is quantified in structure **7** (the methyl groups are omitted from the following structures for clarity). The bond lengths in the allyl-like portion across the



top of the drawing are relatively short, that is, approximately 1.40 Å (benzene-like), as expected for charge delocalization. The other bond lengths are somewhat shorter than a single bond between sp³ carbon atoms (typically ca. 1.54 Å) and

longer than a single bond between unconjugated sp² carbon atoms (typically ca. 1.48 Å).

Several valence bond structures may be considered.^[3] The fully delocalized form **8**, which would suffer from antiaromaticity, is eliminated because of the observed irregularity of the pentagon. Structure **9** requires a localized cation at C1 and localized double bonds, whereas the observed C3-C4 and C1-C5 lengths are closer to single bonds. Structure **10** best describes the C1-C2-C3 (allyl-like) portion. The observed C4-C5 bond is closer to a single bond and is poorly depicted by all the structures.

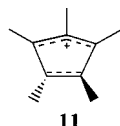
The best reported calculations on the pentamethyl derivative^[16] indicate strong bond alternation resembling **9**, with a nearly single C4-C5 bond (1.56 Å) but no pyramidalization at these carbon atoms. Our own calculations on the pentamethyl derivative^[17,18] at higher level, however, favor structure **10**, with lengths of 1.38 and 1.39 Å (observed 1.406(6) and 1.394(6) Å) for the bonds (C1-C2, C2-C3) in the allyl portion, 1.52 and 1.53 Å (observed 1.500(6) and 1.481(6) Å) for the next adjacent bonds (C1-C5 and C3-C4), and 1.36 Å (observed 1.510(6) Å) for the bond (C4-C5) opposite the allyl portion. All calculations^[16,17] have indicated a planar structure. Thus the major differences between our calculations and observations are an observed lengthening of C4-C5 by 0.15 Å and pyramidalization of C4 and C5.^[19]

The solid-state ¹³C NMR spectrum reflects the nonequivalence of the five ring carbon atoms in the crystal. As a result, all ten carbon atoms in the molecule give distinct or nearly distinct peaks. There are five methyl resonances in the region $\delta = 7-22$. The cationic region contains two equal peaks at $\delta = 243$ and 250, corresponding to C1 and C3. The central carbon atom (C2) in the allyl-like fragment gives a sharp signal at $\delta = 153$, indicative of the absence of charge at the nodal position of the allyl group. The resonances for C1-C2-C3 closely resemble those for the 1,3-dimethylallyl cation ($\delta = 236$ and 147).^[20] Finally, a peak at $\delta = 60$ is intermediate between the normal alkane and alkene regions and fits well for the pyramidalized carbon atoms, C4 and C5. Higher symmetry is indicated in solution, as the C1/C3 resonances appear at the approximate average positions of those in the solid.

The unsaturated region of the ¹³C NMR spectrum is best attributed to the allyl fragment of **10** (two carbon atoms bearing positive charge, plus one on the node). Structure **9** has only one carbon atom bearing positive charge. Thus NMR spectroscopic analysis confirms the conclusions from the crystal structure that **10** best describes the pentamethylcyclopentadienyl cation.

To probe the spin multiplicity of this cation, we examined pure crystals and diluted powder by ESR spectroscopy. No significant signals were obtained at either 77 or 298 K. A triplet state thus is unlikely. The sharpness of the NMR signals both in the solid and in solution strongly supports the absence of unpaired electron spins, which should have broadened the signals. The pentamethylcyclopentadienyl cation therefore appears to be a stable singlet molecule. Our calculations^[17] found the planar singlet state of the pentamethyl derivative to be lower by 1.5 kcal mol⁻¹ than the symmetrical (*D*_{5h}) triplet state.

Crystallography, NMR spectroscopy, and theory support a structure most closely resembling **10**. The pyramidalicity of C4 and C5 and the Me-C4-C5-Me dihedral angle in the crystal (107°), however, indicate significant deviations from a double bond. The estimated barrier to torsion around the C4-C5 bond is quite small, perhaps under 100 cal mol^{-1} . Thus in both calculation and observation, this formally double bond is very unusual. The pyramidalicity seems to imply a fourth coordination, yet there is no fourth atom within the sum of the ionic radii. The closest atom to C4 is F6 ($3.092 \text{ \AA}$) from the counteranion (Figure 1), and the closest atom to C5 is F14 ($3.394 \text{ \AA}$) from the second anion in the asymmetric unit. Fluorine atoms at $3.1-3.4 \text{ \AA}$ distance can provide only a very small perturbation to pyramidalize C4 and C5 and lengthen C4-C5. In the solid state, there is a fluorine atom on the anion close to a hydrogen atom on each of the methyl groups on C4 and C5 ($\text{H12} \cdots \text{F20 } 2.70 \text{ \AA}$, $\text{H14} \cdots \text{F18 } 2.50 \text{ \AA}$). These distances would be about $1 \text{ \AA}$ shorter if the ring substituents moved into the plane of the ring. Crystal packing between the anion and the cation pyramidalizes C4 and C5, a distortion permitted by the weak π bonding. These are noncovalent, nonbonded interactions. The resulting deformations are a tradeoff between coulombic attractions and nonbonded repulsions.



In summary, we have observed that the pentamethylcyclopentadienyl cation is a stable singlet with a largely localized electronic structure best described by **11**.

Received: January 3, 2002 [Z18473]

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Asymmetric Chelated Claisen Rearrangements in the Presence of Chiral Ligands—Scope and Limitations

Uli Kazmaier,* Heike Mues, and Achim Krebs^[a]

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

Abstract: Claisen rearrangements of glycine crotyl ester enolates in the presence of chelating metal salts and chiral ligands provide γ,δ -unsaturated amino acids in a highly stereoselective fashion. Best results are obtained with electron withdrawing protecting groups, isopropylates of aluminum and magne-

sium, and the cinchona alkaloids as chiral ligands. While the use of quinine gives rise to the (2*R*)-configured amino

Keywords: alkaloids • amino acids • asymmetric synthesis • chelates • Claisen rearrangements

acids, quinidine provides the opposite enantiomer. The different enantiomers can also be obtained by using only one of the chiral ligands by simply changing the reaction conditions. A mechanistic rationale for the stereochemical outcome of the reaction is given, which is supported by several experiments.

Introduction

Sigmatropic rearrangements have received much attention for organic synthesis during the last decades, especially because they belong to the most powerful tools for stereoselective C–C-bond formations.^[1] Even though Claisen reported the first rearrangement of this type in 1912^[2] it took quite a while until the Claisen rearrangement became the most synthetically useful [3,3]-sigmatropic rearrangement. The popularity of this stereoselective process resulted in further improvements and the development of variations, such as the Carrol,^[3] Eschenmoser-,^[4] Johnson-,^[5] Ireland-,^[6] Reformatsky-,^[7] ketene-Claisen rearrangement,^[8] as well as carbanion accelerated versions.^[9] During the last years we developed a version especially suitable for the synthesis of amino acids, proceeding via chelated amino acid ester enolates.^[10] The chelate Claisen rearrangement is an alternative to the oxazole rearrangement developed by Steglich et al. previously.^[11]

Based on the concerted reaction mechanism and the high preference for a chairlike transition state, Claisen rearrangements are extremely suitable for chirality transfer.^[1] Therefore it is not surprising that diastereoselective versions have been developed for nearly all types of Claisen rearrange-

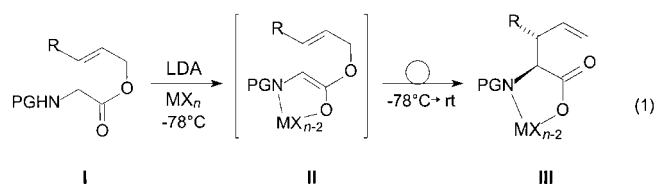
ments.^[12, 13] In the chelate Claisen rearrangement chiral allylic alcohols can be used to control the stereochemical outcome of the reaction.^[14] On the other hand it is also possible to integrate a glycine unit into a peptide and to introduce a side chain by a chelate Claisen rearrangement onto the peptide, while the configuration of the new formed stereogenic center is controlled by the peptide chain.^[15] Even more interesting, in comparison to these auxiliary or substrate controlled reactions, are rearrangements in the presence of chiral modified Lewis acids. The first example of a Lewis acid catalyzed asymmetric Claisen rearrangement was described by Yamamoto et al. in 1990,^[16] while shortly after that Corey et al. reported on the first ester enolate Claisen rearrangement^[17] using chiral boron enolates.^[18] The same chiral boron reagent was used recently by Taguchi et al. for the Claisen rearrangement of fluorinated allyl vinyl ether.^[19] We found that chelated amino acid ester enolates can also be subjected to a rearrangement in the presence of chiral ligands, such as the cinchona alkaloids, giving rise to γ,δ -unsaturated amino acids with excellent diastereoselectivity and high enantiomeric excess.^[20] All these protocols need at least one equivalent of the chiral inductor, probably because the rearrangement product is more Lewis basic than the starting material and therefore forms a stronger complex with the chiral Lewis acid. From a synthetic point of view it would be very welcome to find a catalytic process, requiring only catalytic amounts of chiral ligands. But therefore, it is necessary to find ligands showing a significant ligand acceleration in order to get good chirality transfer, what is not a trivial issue. The first success with this respect was reported by Overman et al. on a palladium(II)-catalyzed rearrangement of

[a] Prof. Dr. U. Kazmaier, Dr. H. Mues, Dr. A. Krebs
Fachrichtung 8.12 Organische Chemie
Universität des Saarlandes
Im Stadtwald, Geb. 23.2, 66041 Saarbrücken (Germany)
Fax: (+49) 681-302-2409
E-mail: u.kazmaier@mx.uni-saarland.de

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achiral allyl imidates, in the presence of chiral ligands.^[21] This is an interesting approach for the stereoselective construction of new C–N bonds. On a comparable catalytic C–C-bond formation was not reported so far.

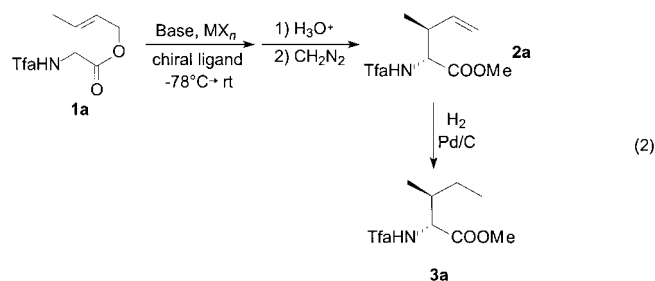
Herein we report on our investigations of chelate Claisen rearrangements of amino acid esters in the presence of chiral ligands. Allylic esters of *N*-protected amino acids **I** (PG: protecting group) undergo a clean Claisen rearrangement when treated with strong bases such as LDA or LHMDS in the presence of metal salts (MX_n).^[10] Probably a chelate complex **II** is formed in the first stage which undergoes Claisen rearrangement during warm up to room temperature [Eq. (1)]. In general, the rearrangement starts in the range of



–30 to –20 °C. As a result of a chairlike transition state, the *syn*-configured product **III** is formed preferentially. If a chelate complex such as **II** really exists, one might expect to find an influence of a chiral ligand, coordinating to the metal, on the stereochemical outcome of the rearrangement.

Results and Discussion

We found, that the chelate Claisen rearrangement is compatible with most common *N*-protecting groups, except base-labile groups such as Fmoc. The rearrangement is widely flexible with respect of the metal salts used, and it tolerates a wide range of substitution pattern in the allyl moiety and the amino acid as well.^[10] As reference compound for the optimization of the reaction parameters we chose trifluoroacetyl (Tfa)-protected glycine crotyl ester **1a** as starting material. Stereoisomers of 3,4-dehydro isoleucine are obtained by a Claisen rearrangement, and are subsequently compared with natural samples of isoleucine **3a** after esterification and hydrogenation [Eq. (2)].^[22] The Tfa-pro-



tecting group was used to have an easy determination of the relative and absolute configuration of the rearrangement product by GC using a chiral column (Chirasil-Val).^[23]

We found that LHMDS in general is superior to LDA regarding the yield. If the chelated Tfa-protected ester is

stirred at 0 °C or room temperature for some time, LDA can cause cleavage of the Tfa-protecting group, a side reaction which is not observed with the less nucleophilic LHMDS.

During an intensive ligand and metal screening we investigated several popular combinations such as Ti⁴⁺/Taddol,^[24] Sn²⁺/diamines,^[25] and Zn²⁺/amino alcohols.^[26] Unfortunately none of them gave a significant chiral induction (<5% *ee*), although the yield was good in most cases. This is not surprising, because ZnCl₂ is the metal salt of choice for most Claisen rearrangements, with respect to yield and diastereoselectivity as well. But obviously the amino alcohols investigated did not form complexes suitable for chirality transfer. During our metal tuning we made an interesting observation: Al(OiPr)₃, a metal salt, which always failed in all reactions of chelated enolates investigated so far, gave the best results concerning yield and selectivity. Amino alcohols (Figure 1) were the chiral ligands of choice and the results obtained are collected in Table 1.

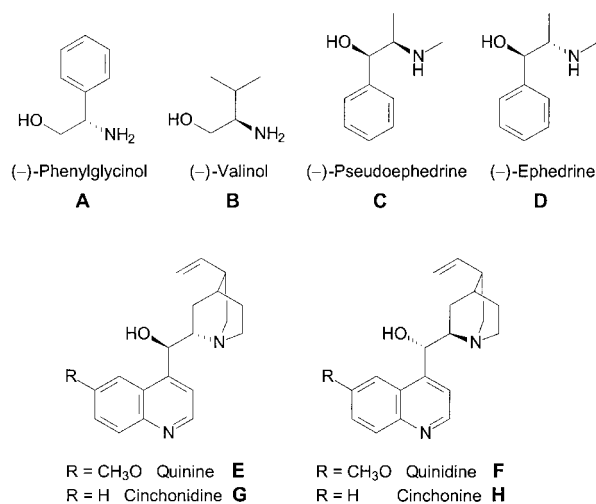


Figure 1. Chiral ligands used in asymmetric Claisen rearrangements.

Table 1. Influence of chiral ligands on chelate Claisen rearrangements of ester **1a** using Al(OiPr)₃ as a chelating metal salt.^[a]

Ligand	Equiv	Product	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]	Configuration
1 –	–	<i>rac</i> - 2a	96	85	0	–
2 A	1.2	<i>rac</i> - 2a	68	85	1	–
3 B	1.5	<i>ent</i> - 2a	73	87	4	(2 <i>S</i> ,3 <i>R</i>)
4 C	1.2	2a	30	94	14	(2 <i>R</i> ,3 <i>S</i>)
5 D	1.2	2a	70	96	27	(2 <i>R</i> ,3 <i>S</i>)
6 <i>ent</i> - D	1.2	<i>ent</i> - 2a	72	96	27	(2 <i>S</i> ,3 <i>R</i>)
7 <i>ent</i> - D	0.6	<i>ent</i> - 2a	75	95	24	(2 <i>S</i> ,3 <i>R</i>)
8 <i>ent</i> - D	0.2	<i>ent</i> - 2a	69	91	10	(2 <i>S</i> ,3 <i>R</i>)
9 E	0.6	2a	57	90	38	(2 <i>R</i> ,3 <i>S</i>)
10 E	1.0	2a	98	94	67	(2 <i>R</i> ,3 <i>S</i>)
11 E	2.0	2a	98	97	81	(2 <i>R</i> ,3 <i>S</i>)
12 E	2.5	2a	98	98	87	(2 <i>R</i> ,3 <i>S</i>)
13 E	4.0	2a	79	97	84	(2 <i>R</i> ,3 <i>S</i>)
14 F	2.5	<i>ent</i> - 2a	96	98	86	(2 <i>S</i> ,3 <i>R</i>)
15 G	2.5	2a	36	97	64	(2 <i>R</i> ,3 <i>S</i>)
16 H	2.5	<i>ent</i> - 2a	42	97	78	(2 <i>S</i> ,3 <i>R</i>)
17 E -OMe	2.5	<i>rac</i> - 2a	97	90	0	–

[a] Reaction conditions: 1) **1a**, 1.1 equiv Al(OiPr)₃, × equiv ligand, 5 equiv LHMDS, –78 °C → RT; 2) CH₂N₂, Et₂O, RT.

Variations of chiral ligands: The *ee* values obtained with simple amino alcohols (**A**, **B**) were still very low (Table 1, entries 1 and 2); evidently the chiral center at the amino group does not play an important role. Introduction of a second chiral center at the hydroxy group resulted in a significant increase of the enantio- and diastereoselectivity as well, obviously the influence of this center on the stereochemical outcome of the reaction is much stronger. Switching from (–) valinol (**B**) to (–) pseudoephedrine (**C**) gave the enantiomeric rearrangement product with an increased diastereoselectivity, although the configuration of the amino group in the ligand was the same. Obviously the stereodirecting effect of the two stereogenic centers in pseudoephedrine is contrary (mismatched case). Indeed, after inversion of one of the centers by using the ephedrines (**D** and *ent*-**D**) (entries 5 and 6) the *ee* values were nearly twice as high. Also the yields were much better. Depending on the ephedrine used, both enantiomers of the amino acid can be obtained easily. Even the enantiomeric excess was still moderate, we undertook a first investigation regarding ligand acceleration. Reducing the amount of ligand from 1.2 to 0.6 equivalents had no significant effect (entry 7) but a further reduction to 0.2 equivalents resulted in a dramatic drop, especially of the enantiomeric excess (entry 8). Although there might be a weak ligand acceleration, this effect is not strong enough for a successful catalytic application.

A further improvement was observed by increasing the sterical bulk of the substituents at the amino alcohol moiety. The same relative configuration as in the ephedrines is found in the cinchona alkaloids (**E**–**H**). For example quinine, which is related to (–)-ephedrine, gave the same major isomer, although in much better yield and enantioselectivity (entries 9–13). Unfortunately again no ligand acceleration was observed in this case; the acceleration was even worse in comparison to ephedrine. Quinine significantly reduces the reactivity of the enolate. While a rearrangement without a ligand takes place already at –30 to –20°C, with quinine $\approx 0^\circ\text{C}$ are necessary. Because of this ligand deceleration effect, an excess of quinine is necessary to suppress a reaction pathway via a ligand free chelate complex. By far the best results are obtained with 2.5 equivalents of quinine (entry 12). A further increase of the quinine concentration had no significant effect on the *ee*; in addition the yield dropped (entry 13). While quinine gives rise to the (*R*)-configured amino acid, the (*S*)-isomer can be obtained by using the pseudoenantiomeric ligand quinidine (**F**). The yields and selectivities with these two ligands are absolutely identical. Obviously the vinyl group at the bicyclic subunit has no influence on the rearrangement. Dihydroquinine, obtained by catalytic hydrogenation of quinine, gave also the same results.

Two other cinchona alkaloids which are commercially available are cinchonidine (**G**) and cinchonine (**H**) which differ from the previous ligands only in the lack of the methoxy group on the chinolin nucleus. This methoxy group has a positive effect regarding the solubility of the ligands. While quinine and quinidine are soluble in THF in a 0.3 M range even at –70°C, a suspension is obtained with ligands **G** and **H** under the same conditions. This might explain the lower yields and enantioselectivities obtained with these

ligands (entries 15 and 16). A lower concentration of solubilized ligand results in lower *ee* values as shown previously.

The amino alcohols probably bind as bidentate ligands towards the chelated metal ion. Methylation of quinine at the hydroxy group resulted in a completely racemic mixture of the rearrangement product (entry 17), but the diastereoselectivity was better than in reactions without an additional ligand.

Variations of the N-protecting groups: In terms of an easy and reliable determination of the stereochemical outcome of the reaction we chose the trifluoroacetyl group as protecting group on the nitrogen. But one might expect a strong influence of this protecting group on the reaction. Therefore, we investigated the influence of the steric and electronic effect of several protecting groups [Eq. (3), Table 2]. By far the best results were obtained with the initially applied Tfa

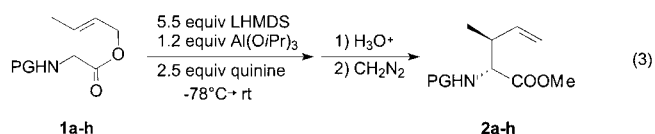


Table 2. Influence of the protecting group (PG) on chelate Claisen rearrangements of ester **1a–h**.^[a]

	PG	Product	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]
1	Tfa	2a	98	98	87
2	Bz	2b	50	95	60
3	Cbz	2c	88	90	49
4	Tos	2d	98	90	46
5	Boc	2e	78	90	16
6	Ac	2f	23	85	13
7	<i>p</i> -F-Bz	2g	77	99	58
8	Pfp	2h	93	99	87

[a] Reaction conditions: 1) **1**, 1.1 equiv $\text{Al}(\text{O}i\text{Pr})_3$, 2.5 equiv quinine, 5 equiv LHMDS, $-78^\circ\text{C} \rightarrow \text{RT}$; 2) CH_2N_2 , Et_2O , RT.

group (entry 1), while the other protecting groups gave significantly worse results, in terms of both yield and selectivity. Good yields are also obtained with Cbz- and Tosyl-protected crotyl esters (entries 3 and 4), while the benzoyl protected derivatives gave good selectivities. Quite surprising was the big difference between the trifluoroacetyl and the acetyl protected esters (entry 1 vs. 6). From a steric point of view there should be no big difference between these two acyl groups and obviously the strong electron withdrawing effect of the fluorine atoms is responsible for the high selectivities observed. Therefore, we decided to have a closer look on this phenomenon and we investigated the rearrangement of fluorinated benzoyl protected esters. Introduction of one fluorine atom (entry 7) into the *para*-position of the benzoyl group resulted in an increased yield and diastereoselectivity, although the enantiomeric excess was nearly constant. But the pentafluorobenzoyl (Pfp) and the trifluoroacetyl protected derivative gave comparable results (entry 8).

Variations of the chelating metal salts: After this successful ligand screening we investigated the influence of the chelating metal salt under these optimized conditions [Eq. (2), 1.1 equiv

metal salt, 2.5 equiv quinine]. The results obtained are listed in Table 3. As mentioned earlier, zinc chloride gave a very clean reaction, providing the expected amino acid in high yield but without significant *ee* (entry 1). Other halides gave better results. Surprisingly even calcium chloride (entry 4),

Table 3. Variation of the metal salts in chelate Claisen rearrangements of ester **1a** to **2a**.^[a]

	Metal Salt	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]
1	ZnCl ₂	95	90	10
2	EtAlCl ₂	97	85	28
3	BCl ₃	93	86	42
4	CaCl ₂	73	96	65
5	MgCl ₂	98	91	69
6	Mg(OEt) ₂	98	96	83
7	Al(O ^{<i>i</i>} Pr) ₃	98	98	87
8	–	95	97	78

[a] Reaction conditions: 1) **1a**, 1.1 equiv MX_m, 2.5 equiv quinine, 5 equiv LHMDs, –78 °C → RT; 2) CH₂N₂, Et₂O, RT.

powderized drying agent, gave a colorless clear solution, which is a clear indication for chelate complex formation. The selectivities obtained were good and comparable to the findings obtained with magnesium chloride (entry 5). Interestingly the “counterion” also has an influence (entry 5 vs. 6). Obviously alcoholates are the metal salts of choice giving by far the best results (entries 6 and 7). This was quite a surprise, because alcoholates never gave clean reactions of these enolates before.

For example, in aldol reactions, Michael additions or Claisen rearrangements without chiral ligand the addition of these alcoholates had no influence on the outcome of the reaction, in comparison to the reaction of the lithium enolate. Therefore we had some doubt concerning the transmetalation of the enolates with these metal salts and we investigated also the rearrangement of the lithium enolate (entry 8). Without a chiral ligand, these lithium enolates decompose and do not undergo a Claisen rearrangement. But in the presence of quinine the rearrangement product was obtained in excellent yield and high stereoselectivity.

Although the *ee* values are higher in the presence of the magnesium and aluminium alcoholates, the results are in the same range. Obviously the chiral ligand is able to stabilize the lithium enolate, and we assume that it is this lithium enolate which undergoes the Claisen rearrangement. Probably a bimetallic complex is formed with the bidentate ligand quinine (or quinidine, respectively) coordinating to the lithium enolate (Figure 2). The incorporation of a second

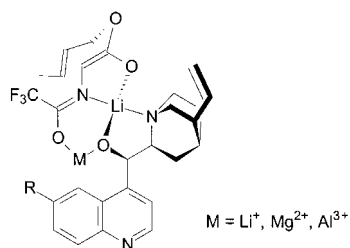
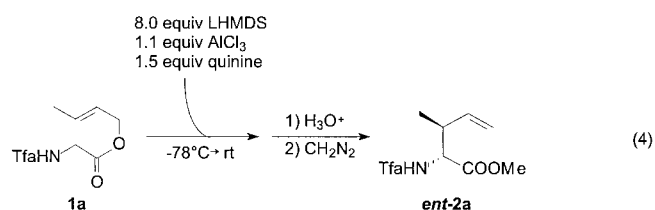


Figure 2. Bimetallic chelate complex.

metal ion M (Li⁺, Al³⁺, Mg²⁺) into the complex should stabilize this complex by forming a very rigid structure, in which one face of the enolate is shielded by the bicyclic substructure of the quinine. This would explain the high *ee* values obtained with this system. Obviously the alcoholates are not involved in enolate formation directly, but they have an influence on the reaction via the bimetallic complex. The similar *ee* values obtained might be explained by similar ion radii of the metal ions (Li⁺: 0.60 Å, Mg²⁺: 0.65 Å, Al³⁺: 0.51 Å).

If this working model is correct, one should find strong effects if the chelating lithium ion is replaced by other metal ions. Indeed, if the reaction was carried out in the absence of lithium, the selectivity dropped dramatically. No rearrangement product at all was obtained when KHMDS was used as a base. With NaHMDS the yield (18 %) and selectivities (85 % *ds*, 14 % *ee*) were low, but could be increased by adding LiCl to the reaction mixture (78 % yield, 96 % *ds*, 59 % *ee*). This clearly demonstrates the importance of the lithium ion for the complex formation.

To proof the position of the lithium ion, we modified the reaction conditions in order to generate the aluminium enolate. For this purpose LHMDs was added to a suspension of AlCl₃ in THF at –20 °C [Eq. (4)]. This mixture was stirred



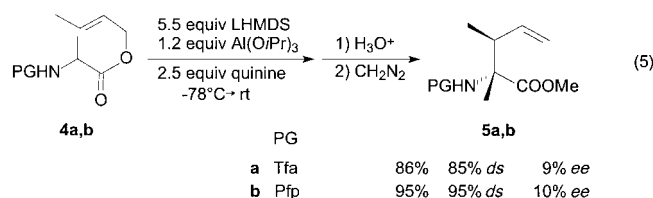
for 10 min at room temperature to form aluminium amide complexes before the quinine was added. After stirring the mixture for further two hours at room temperature, the clear pale yellow solution was added to the crotyl ester at –78 °C. Under these modified conditions highly surprising results were obtained: The rearrangement product was formed in good yield (74 %) with only moderate diastereoselectivity (85 % *ds*). The enantiomeric excess was rather high (71 % *ee*), but what was most astonishing, the opposite enantiomer of the amino acid was obtained when the reaction was carried out under standard conditions. Exactly the same was true with the pentafluorobenzoyl protected derivative, which gave comparable results.

Obviously the chiral aluminium enolate complex prefers another complex geometry than the corresponding lithium complex. Therefore it is now possible to generate both enantiomers of the rearrangement product by using the same substrate, the same chiral ligand, the same base, and the same metal ions by simply changing the reaction conditions.

Variations of the amino acid: In general, the chelate Claisen rearrangement can be applied not only to esters of glycine, but also to those of most other amino acids, even those with functionalized side chains.^[27] In the rearrangement without a chiral ligand, the yields and selectivities are comparable to glycine esters. But if our assumption of a bimetallic enolate

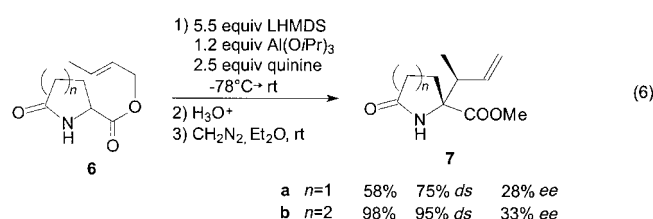
complex was correct, a substituent at the α -position of the enolate should interact with the N-protecting group in this planar complex, resulting in a destabilization of the complex and a lower enantiomeric excess.

Exactly this effect was observed in the rearrangement of the corresponding alanine esters **4** [Eq. (5)]. Although the yields



were good, the diastereoselectivity was moderate to good and the same as in the reactions without quinine (control experiment). The very low *ee* values (< 10%) are a clear indicate for a collapse of a chiral complex proposed.

On the other hand, if the steric interaction described in here destabilizes the complex, a connection between the *N*-protecting group and the side chain should favor the bimetallic complex by fixation of the spatial orientation of the amino acid ester. For this purpose we synthesized crotyl esters starting from pyroglutaminic acid (**6a**) and 6-oxopipicolinic acid^[28] (**6b**) and subjected them to our rearrangement conditions [Eq. (6)]. Indeed, the enantioselectivity could be



increased significantly in comparison to the open chain derivatives **4**, even those bearing fluorinated protecting groups. Although the *ee* values are “only” in the range of 30%, one should keep in mind that these derivatives do not contain electron withdrawing groups and that the results should better be compared with those of the acetyl derivatives (Table 2, entry 6) rather than the trifluoroacetylated esters.

Conclusion

In summary, we have shown that cinchona alkaloids are suitable ligands for asymmetric Claisen rearrangements of achiral chelated enolates. This protocol allows the synthesis of both enantiomers of γ,δ -unsaturated amino acids not only by switching between the alkaloids quinine and quinidine, but also by changing the reaction conditions.

Experimental Section

General remarks: All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled

from sodium/benzophenone, CH_2Cl_2 from CaH_2 and stored over molecular sieves. The products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of EtOAc and hexanes were generally used as eluents. TLC: commercially precoated Polygram SIL-G/UV 254 plates (Machery–Nagel). Visualization was accomplished with UV light and KMnO_4 solution. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR: Bruker AC-300 or Bruker DRX-500 spectrometer. Selected signals for the minor diastereomers are extracted from the spectra of the diastereomeric mixture. Enantiomeric and diastereomeric excesses were determined on a HP5890 Series II gaschromatograph with a Chirasil-Val capillary column, as well as by analytical HPLC using a Daicel “Chiralcel OD-H”, column (flow: 0.5 mL min^{-1}) and a Knauer UV detector. Optical rotations were measured on a Perkin–Elmer polarimeter PE 241. Elemental analysis were carried out at the Department of Chemistry, University of Heidelberg.

General procedure for the preparation of allylic esters: Dicyclocarbodiimide (2.46 g, 12 mmol) and DMAP (125 mg, 1 mmol) were added to a solution of the allylic alcohol (10 mmol) in methylene chloride (30 mL) at 0 °C. The clear solution was cooled to –20 °C, before the protected amino acid (10 mmol) was added after 5 min. The mixture was allowed to warm to room temperature overnight. After filtration of the precipitate, the organic phase was extracted with 1N KHSO_4 solution, sat. NaHCO_3 solution and with brine. Drying of the organic layer over Na_2SO_4 and evaporation of the solvent gave crude ester which was purified by flash chromatography (hexanes/ethyl acetate).

N-Trifluoroacetyl glycine crotyl ester (1a): Ester **1a** was obtained in a 45 mmol scale according to the general procedure for esterifications in 82% yield. Crystallization from methylene chloride/hexanes gave colorless needles. M.p. 48–49 °C; ^1H NMR (300 MHz, CDCl_3): δ = 1.72 (d, J = 6.8 Hz, 3H, CH_3), 4.11 (d, J = 5.1 Hz, 2H, NCH_2), 4.61 (d, J = 6.9 Hz, 2H, OCH_2), 5.58 (dq, J = 17.4, 6.8 Hz, 1H, CHCH_3), 5.84 (dt, J = 17.4, 6.9 Hz, 1H, CH_2CH), 6.96 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl_3): δ = 17.66 (CH_3), 41.38 (NCH_2), 66.80 (OCH_2), 115.6 (q, J = 286.7 Hz, CF_3), 123.9 (CH_2CH), 133.0 (CHCH_3), 157.2 (q, J = 38.0 Hz, CON), 168.0 (COO); elemental analysis calcd (%) for $\text{C}_8\text{H}_{10}\text{F}_3\text{NO}_3$ (225.2): C 42.67, H 4.48, N 6.22; found: C 42.82, H 4.61, N 6.30.

General procedure for Claisen rearrangements in the presence of chiral ligands: A LHMDS solution was prepared by adding 1.55 *m*-n-buthyllithium in hexane (1.6 mL, 2.5 mmol) at –20 °C under argon to hexamethyldisilazane (470 mg, 2.9 mmol) in dry THF (1.5 mL) and stirring for 20 min. The *N*-protected glycine crotyl ester **1** (0.5 mmol), $\text{Al}(\text{O}i\text{Pr})_3$ (0.55 mmol) and the ligand (1–1.25 mmol) were dissolved under argon in dry THF (5 mL). The mixture was cooled to –78 °C, and the freshly prepared LHMDS solution was added slowly. The reaction mixture was allowed to warm to room temperature within 12 h. After diluting with diethyl ether (50 mL), the reaction mixture was hydrolyzed by addition of 1M aqueous KHSO_4 (25 mL). The organic layer was washed again with 1M KHSO_4 , before the reaction product was extracted with three portions of saturated aqueous NaHCO_3 solution (25 mL each). The basic solution was subsequently acidified by careful addition of solid KHSO_4 to pH 1 and extracted with three portions of diethyl ether (25 mL each). The combined organic extracts were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. For the determination of the enantiomeric and diastereomeric ratios of the product, the residue was treated with diazomethane in ether solution. Subsequent chromatography on silica gel gave the corresponding methyl esters.

(2R,3S)-3-Methyl-2-(trifluoroacetyl amino)-4-pentenoic methyl ester (2a): According to the general procedure for Claisen rearrangements *syn*-ester **2a** was obtained from crotyl ester **1a** (123 mg, 0.5 mmol), $\text{Al}(\text{O}i\text{Pr})_3$ (114 mg, 0.55 mmol) and quinine (405 mg, 1.25 mmol) (98% yield, 87% *ee*, 98% *ds*) as a colorless oil; $[\alpha]_D^{20}$ = –54.4° (c = 2.0, CHCl_3 , 87% *ee*, 98% *ds*); ^1H NMR (300 MHz, CDCl_3): δ = 1.09 (d, J = 7.0 Hz, 3H, CHCH_3), 2.73 (ddq, J = 8.5, 7.0, 6.9 Hz, 1H, CHCH_3), 3.77 (s, 3H, OCH_3), 4.63 (dd, J = 8.5, 5.0 Hz, 1H, NCH), 5.09 (dd, J = 17.1, 1.1 Hz, 1H, CHCH_2), 5.14 (dd, J = 10.5, 1.1 Hz, 1H, CHCH_2), 5.65 (ddd, J = 17.1, 10.5, 6.9 Hz, 1H, CHCH_2), 6.84 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl_3): δ = 15.4 (CHCH_3), 40.6 (CHCH_3), 52.6 (OCH_3), 56.1 (OCH_3), 115.6 (q, J = 287 Hz, CF_3), 117.3 (CHCH_2), 137.3 (CHCH_2), 156.6 (q, J = 38 Hz, CON), 170.3 (COO); *anti*-**2a** (selected signals): ^1H NMR (300 MHz, CDCl_3): δ = 1.14 (d, J = 7.0 Hz, 3H, CHCH_3), 2.84 (m, 1H, CHCH_3), 3.80 (s, 3H, OCH_3), 6.75 (brs, 1H, NH); ^{13}C NMR (75 MHz, CDCl_3): δ = 15.8 (CHCH_3), 40.2 (CHCH_3), 52.7

(OCH₃), 56.5 (NCH), 117.8 (CHCH₂), 136.7 (CHCH₂); GC (Chirasil-Val, 80 °C, isothermic): *t_R* (2*R*,3*R*) = 6.79 min, *t_R* (2*R*,3*S*) = 7.64 min, *t_R* (2*S*,3*S*) = 7.99 min, *t_R* (2*S*,3*R*) = 8.66 min; elemental analysis calcd (%) for C₉H₁₂NO₃F₃ (242.2): C 45.19, H 5.06, N 5.86; found: C 45.14, H 5.07, N 5.73.

(2*S*,3*R*)-3-Methyl-2-(trifluoroacetyl-amino)-4-pentenoic methyl ester (ent-2a)

1) *syn*-Ester *ent*-2a was obtained according to the general procedure for Claisen rearrangements from crotyl ester **1a** (123 mg, 0.5 mmol), Al(O*i*Pr)₃ (114 mg, 0.55 mmol) and quinidine (405 mg, 1.25 mmol) as a colorless oil (97% yield, 87% *ee*, 98% *ds*). [α]_D²⁰ = +53.6° (*c* = 2.0, CHCl₃, 87%, 98% *ds*).

2) Aluminum chloride (65 mg, 0.49 mmol) was suspended in THF (2 mL) at 0 °C. The suspension was cooled to –20 °C before a solution of LHMDs (8 mL, 3.55 mmol) was added. The cooling bath was removed and the mixture was stirred for 10 min. After cooling to –20 °C, a solution of quinine (216 mg, 0.67 mmol) in THF (3 mL) was added slowly. The mixture was stirred for 2 h at RT. The resulting clear yellow solution was added via syringe to a solution of ester **1a** (100 mg, 0.44 mmol) in THF (2 mL) at –78 °C. The mixture was allowed to warm to room temperature overnight, and the workup was carried out as described in the general procedure for Claisen rearrangements. Ester *ent*-2a was obtained as a colorless oil (74% yield, 71% *ee*, 85% *ds*). [α]_D²⁰ = +40.3° (*c* = 1.7, CHCl₃, 71% *ee*, 85% *ds*); NMR and GC data see **2a**; elemental analysis calcd (%) for C₉H₁₂NO₃F₃ (242.2): C 45.19, H 5.06, N 5.86; found: C 45.34, H 4.98, N 5.83.

Acknowledgement

Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie as well as the Institute of Organic Chemistry at the University of Heidelberg is gratefully acknowledged. We also thank Buchler GmbH for generous gifts of cinchona alkaloids.

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Received: November 9, 2001 [F3677]

199 °C. Elemental analysis (%) calcd for $C_{36}H_{48}N_2O$: C 82.39, H 9.22, N 5.34; found: C 80.43, H 9.37, N 5.12; ^1H NMR (C_6D_6 , 300 MHz, 25 °C, TMS): δ = 1.50 (s, tBu, 18H), 2.23 (s, Me, 18H), 2.36 (s, Me, 3H), 6.49 (s, C=CH, 2H), 6.63 (brs, NCHN, 1H), 6.88 (s, *m*-ArH, 4H), 7.17 (s, ArH, 2H) ppm.

5: **1** (0.30 g, 1.0 mmol) and **3** (0.17 g, 1.0 mmol) were dissolved in toluene (5 mL) by gentle warming. Overnight and at room temperature the resulting solution yielded a crop of orange crystals. First batch yield 0.18 g (38%), mp. 158–162 °C. Elemental analysis (%) calcd for $C_{33}H_{35}N_3$: C 83.68, H 7.45, N 8.87; found: C 82.85, H 7.37, N 8.92; ^1H NMR (C_6D_6 , 300 MHz, 25 °C, TMS): δ = 2.25 (s, *o*-Me, 12H), 2.26 (s, *p*-Me, 6H), 5.92 (brs, NH, 1H), 6.55 (s, C=CH, 2H), 6.90 (s, *m*-MesH, 4H), 6.96, 7.18, 7.26 (m, ArH, 10H) ppm.

Received: January 14, 2002 [Z18515]

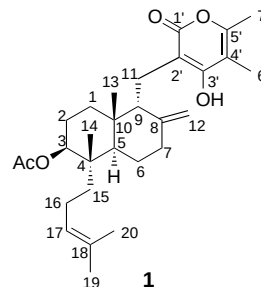
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- [4] a) Crystal data for **4**: $C_{167}H_{229}N_8O_4$, colorless block of dimensions $0.2 \times 0.2 \times 0.1$ mm³, trigonal, $P\bar{3}$, $a = 27.008(9)$, $c = 17.684(9)$ Å, $V = 11171(8)$ Å³, $Z = 3$, $\rho_{\text{calcd}} = 1.076$ g cm⁻³. Data collected on a Bruker Smart diffractometer with MoK_{α} radiation ($\lambda = 0.71073$ Å) and ω scans at $T = 100(2)$ K, $2\theta_{\text{max}} = 54.96^\circ$, 121 949 reflections measured, of which 17 075 independent ($R_{\text{int}} = 0.0557$), $\mu = 0.063$ mm⁻¹ (no absorption correction). Structure solved by direct methods (SHELXS-97)^[13] and refined on F^2 by full-matrix least-squares (SHELXL-97)^[13] 867 parameters, $R_1 = 0.0597$ (11 562 data $I > 2\sigma(I)$), $wR_2 = 0.1852$ (all data). H atoms were placed in calculated positions with a riding refinement, except those involved in hydrogen bonding which were refined freely and isotropically. Site occupancy of lattice hexane solvent was estimated to be 0.75 and fixed at that value. b) Crystal data for **5**: $C_{33}H_{35}N_3$, yellow needle of dimensions $0.5 \times 0.3 \times 0.2$ mm³, triclinic, $P\bar{1}$, $a = 9.663(2)$, $b = 10.578(2)$, $c = 14.967(3)$ Å, $\alpha = 80.60(3)$, $\beta = 71.68(3)$, $\gamma = 67.72(3)^\circ$, $V = 1342.3(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.172$ g cm⁻³. Data collected on a Bruker Smart diffractometer with MoK_{α} radiation ($\lambda = 0.71073$ Å) and ω scans at $T = 30(2)$ K, $2\theta_{\text{max}} = 54.34^\circ$, 11 025 reflections measured, of which 5307 independent ($R_{\text{int}} = 0.0285$), $\mu = 0.069$ mm⁻¹ (no absorption correction). Structure solved by direct methods (SHELXS-97)^[13] and refined on F^2 by full-matrix least-squares (SHELXL-97)^[13] 465 parameters, $R_1 = 0.0376$ (4412 data $I > 2\sigma(I)$), $wR_2 = 0.0991$ (all data). All H atoms were refined freely and isotropically. CCDC-161117 and CCDC-161118 (**4** and **5**, respectively) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 123, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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An Efficient Stereoselective Total Synthesis of DL-Sesquicillin, a Glucocorticoid Antagonist**

Fei Zhang and Samuel J. Danishefsky*

Sesquicillin is a C29 isoprenoid-related fermentation product isolated from *Acremonium* sp., strain 132-94.^[1] The compound was first identified through screenings directed at the discovery of new agents that inhibit glucocorticoid-induced gene expression in suitably engineered COS-7 cells ($IC_{50} = 0.1–0.5$ µg). In principle, sesquicillin could function as a glucocorticoid antagonist.^[2] Also, antihypertensive and bronchospasmolytic properties have been ascribed to sesquicillin in patent disclosures.^[3] It is only relatively recently that the gross structure and stereochemistry of sesquicillin have been assigned to be **1**, largely on the basis of detailed NMR spectroscopic measurements. As such, sesquicillin bears a striking resemblance to subglutinols A and B.^[4] We hoped that a total synthesis of sesquicillin would allow access to the natural product and its analogues. In this way, we could begin to evaluate the potential of this particular type of glucocorticoid antagonist in projected applications.



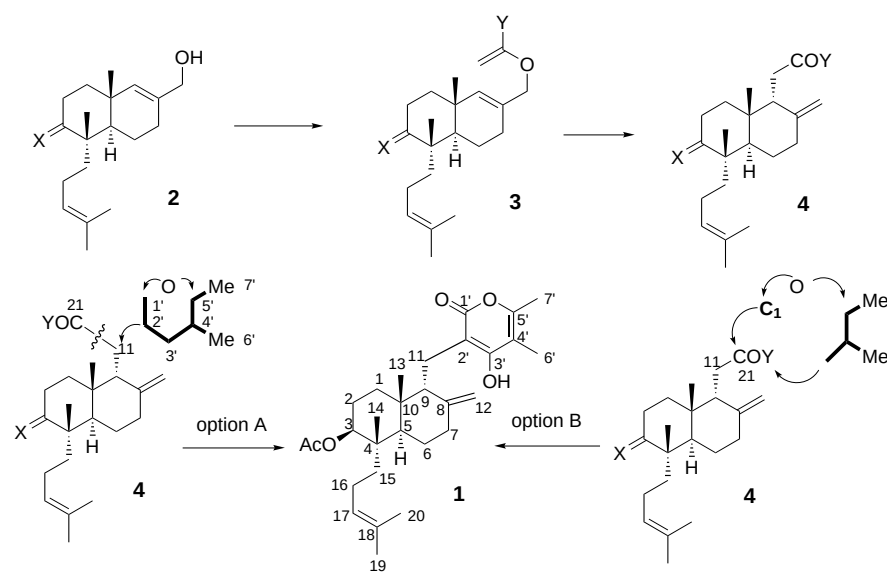
[*] Prof. S. J. Danishefsky, F. Zhang
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY, 10027 (USA)
E-mail: s-danishefsky@ski.mskcc.org

Prof. S. J. Danishefsky
Laboratory for Bioorganic Chemistry
Sloan–Kettering Institute for Cancer Research
1275 York Avenue, Box 106, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691

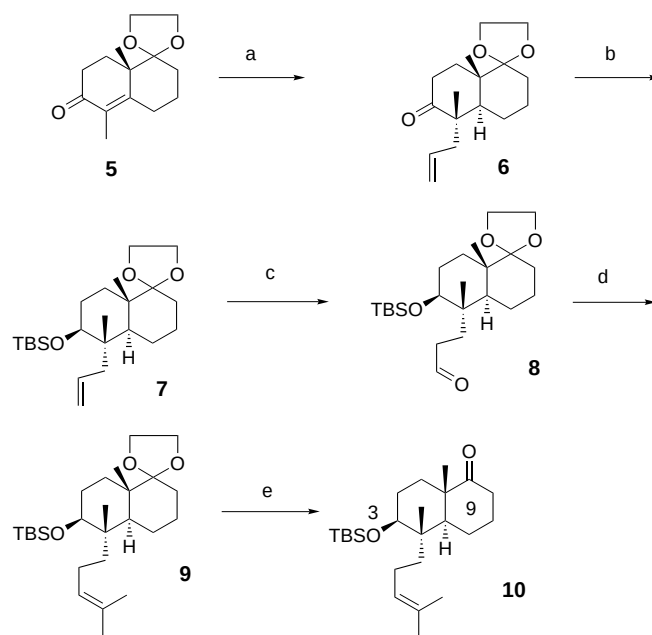
[**] This work was supported by the National Institutes of Health (Grant Number: HL25848). We thank Dr. Yashuiro Itagaki, Columbia University for high-resolution mass-spectral analysis. F.Z. would also like to thank Columbia University and Pharmacia & Upjohn for a graduate fellowship.

Construction of the AB ring sector of the target system was to follow traditional outlines established in numerous *trans*-decalin-based terpenoid and steroid targets.^[5] A serious challenge arises from the need to elaborate a heavily substituted α -pyrone moiety joined to C11, which is axially linked to C9. During these operations, the integrity of the vulnerable *exo* methylene group attached to C8 must be maintained. We hoped to establish the required configuration at C9 relative to the chiral decalin matrix by a [3,3]-sigmatropic bond reorganization originating from suitable derivatization of allylic alcohol **2** (Scheme 1). The rearrangement reaction would produce structure type **4**. It was assumed that in this Claisen-like transformation, the terminal carbon atom (corresponding to C9) would be attacked from its pre-axial (i.e. α) face.^[6] After the rearrangement, we could broadly consider two perceptions for advancement toward **1** (Scheme 1). Option A: C21 in **4** could at some stage be excised through degradation, leaving C11 as the site for appendage. In this case, C11 must be joined to C β (corresponding to 2') of a linear six-carbon-atom construct, which is further branched at C γ (corresponding to the ultimate C4'). Option B: C21 would become C2' of **1** following its interposition between a one-carbon-atom residue (destined to become C1') and a four-carbon-atom ensemble, branched at its β -carbon atom. C α of this ensemble eventually becomes C3' while the β -methyl branch becomes C4' in **1**.

We started with the known ketone **5** (Scheme 2).^[7a] The homoprenyl chain was introduced segmentally,^[7b] reflecting concerns (based on the results of early probes) about direct alkylation of a C4 enolate with a homoprenyl electrophile. In the event, allylation at C4, which exploited the reductively generated kinetic enolate,^[8] gave rise to **6**. Stereospecific reduction of the ketone group and protection of the resulting β -alcohol gave **7**. Chain extension to complete the homoprenyl function proceeded smoothly via aldehyde **8**. Fortunately, PPTS^[9] could be used to deprotect the ketal at C9 without reexposure of the alcohol at C3 (see compound **10**, Scheme 2).



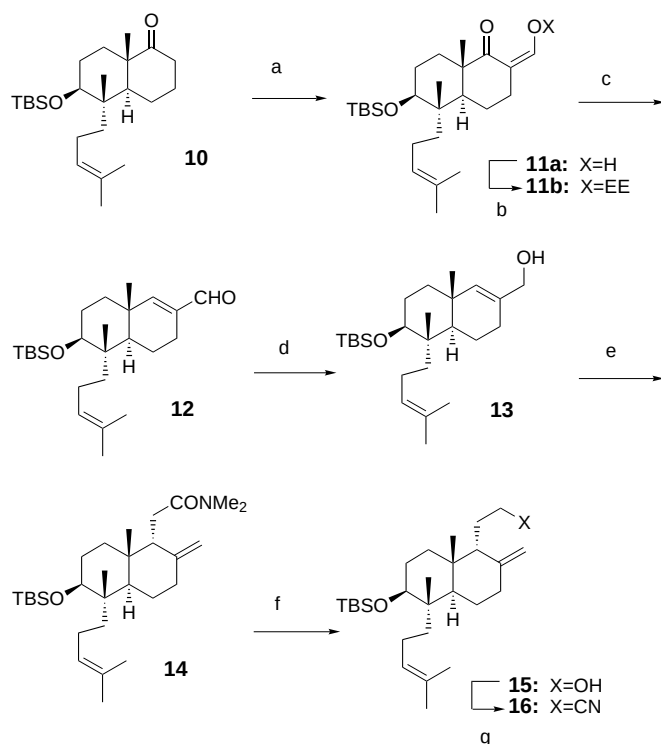
Scheme 1. Strategic pathway to sesquicillin A.



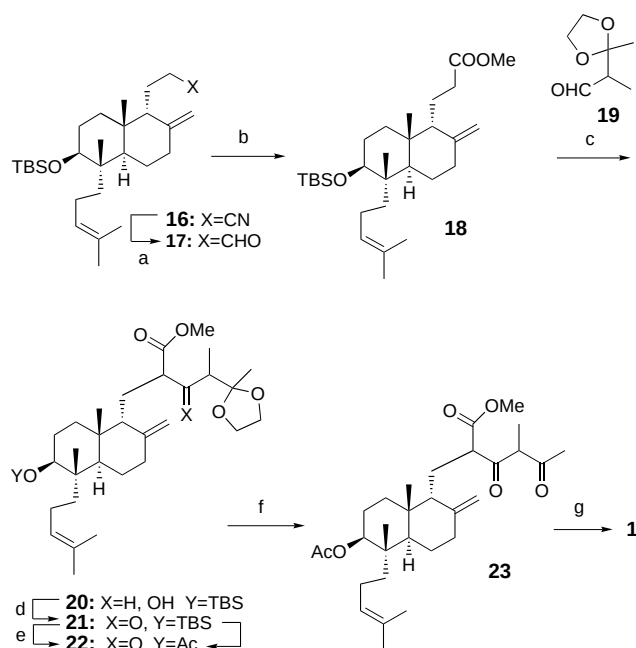
Scheme 2. Reagents and conditions: a) 1. Li/liquid ammonia/THF/*t*BuOH, $-78^{\circ}\text{C} \rightarrow \text{RT}$; 2. allyl bromide (6.25 equiv), 78%; b) 1. NaBH₄/EtOH, $-78^{\circ}\text{C} \rightarrow \text{RT}$; 2. TBSOTf, 2,6-lutidine, CH₂Cl₂, $-78^{\circ}\text{C} \rightarrow \text{RT}$, 83%; c) 1. BH₃·THF, room temperature; 2. NaOH/H₂O₂, reflux; 3. PCC, CH₂Cl₂, 56%; d) isopropyltriphenylphosphonium iodide, *t*BuLi, DMSO, 85%; e) PPTS, acetone, reflux, 96%. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; PCC = pyridinium chlorochromate; DMSO = dimethyl sulfoxide; PPTS = pyridinium *p*-toluenesulfonate.

A specific and functional version of the allylic alcohol that corresponds to hypothetical structure **2** (Scheme 1) was constructed along established lines. Following formylation of **10** with ethyl formate,^[10] the resulting enol of **11a** was protected through a seldom-used mixed *enol acetalization* protocol (Scheme 3).^[11] Reduction of the ketone group of **11b** and acid-induced unmasking of the resulting β -alkoxy allylic alcohol, led to aldehyde **12**. Reduction of the aldehyde function with sodium borohydride afforded **13**, the precursor for the crucial [3,3] sigmatropic rearrangement.

A variety of Claisen-related protocols^[12] were screened for the conversion of **13** into a product of the general type **4** (Scheme 1). Of these, the Eschenmoser variation^[13] shown below was by far the most effective and delivered **14**, which contains the γ,δ -unsaturated *N,N*-dimethylamide function, in high yield with very high stereoselectivity (> 20:1). Attempts to convert the dimethylamide function of **14** into the corresponding acid by direct hydrolysis were, as expected, unrewarding. It seems that C21 (structure **4**) is, in fact, quite hindered. The hindrance is probably even greater at C11. We therefore directed our early efforts to reach **1** toward option B. As shown below, this strategy required particular care to maintain the problem-



Scheme 3. Reagents and conditions: a) NaH/THF, ethyl formate, reflux; b) ethyl vinyl ether, H_3PO_4 (cat); c) 1. $\text{NaBH}_4/\text{EtOH}$; 2. HCl (0.5N), THF/water, 80% over four steps; d) $\text{NaBH}_4/\text{EtOH}$, 100%; e) *N,N*-dimethyl acetamide dimethyl acetal, *m*-xylene, reflux, 87%; f) superhydride, THF, 99%; g) 1. MeSO_2Cl , Et_3N , CH_2Cl_2 ; 2. NaCN , DMF, 100%. DMF = *N,N*-dimethylformamide.



Scheme 4. Reagents and conditions: a) DIBAL-H, hexanes, $-78^\circ\text{C} \rightarrow \text{RT}$; b) 1. NaClO_2 , NaH_2PO_4 , *t*BuOH, H_2O ; 2. TMSCHN_2 , MeOH, benzene, 50% over three steps; c) LDA, **19**, THF, -78°C , 62%; d) DMP, CH_2Cl_2 , 100%; e) 1. $\text{HF}/\text{CH}_3\text{CN}$; 2. Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 83%; f) $[\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2]$, acetone, 97%; g) DBU, benzene, reflux, 61%. DIBAL-H = diisobutylaluminum hydride, TMS = trimethylsilyl, LDA = lithium diisopropylamide, DMP = Dess–Martin periodinane, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

atic *exo* methylene function in place. The congestion problem was solved through the use of relatively nonbulky reagents. Fortunately, the tertiary amide moiety was converted smoothly into the corresponding alcohol **15** through the use of superhydride. Activation of the alcohol as its mesylate set the stage for chain extension by cyanide displacement (see compound **16**, Scheme 3).

We were unable to devise conditions to reach the C21 acid or ester *directly* from **16**, and again circumspection was required. Reduction of nitrile **16** with DIBAL-H led to the corresponding aldehyde **17** in crude form (Scheme 4). Oxidation and esterification of **17** gave methyl ester **18**. Key to our eventual success was the finding that the ester could be deprotonated with LDA. The resulting C2' enolate (sesquicillin numbering) did add to the known aldehyde **19** to give **20**.^[14] Alcohol **20** was oxidized with the Dess–Martin periodinane^[15] to afford **21** as a complex mixture of stereoisomers. Cleavage of the C3 siloxy function^[16] generated an alcohol, which was acetylated to give **22**. The total synthesis phase of this project was then completed by treatment of crude **22** with $[\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2]$, and subsequent DBU-induced enol lactonization of **23** to give DL-sesquicillin (**1**). The ^1H and ^{13}C NMR spectra of synthetic and natural sesquicillin^[1] were identical. Although the total synthesis reported herein is that of racemic **1**, it would be a straightforward matter to prepare either antipode by starting with enantiomerically pure homogenous **5**.^[7a]

We note that the current unoptimized total synthesis of sesquicillin (3.1% overall yield) produces ample amounts of compound for broad-ranging biological studies. It also illustrates the power of the amide acetal version of the Claisen rearrangement (cf. **13** → **14**)^[13] and serves to teach, by example, how serious interactive problems of steric hindrance and labile functionality can be overcome.

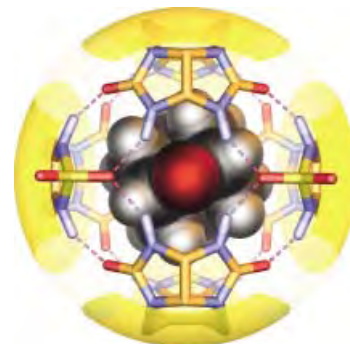
Received: January 16, 2002 [Z18533]

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COVER PICTURE

The cover picture shows adamantane-2,6-dione encapsulated within a hydrogen-bonded capsule made up of four identical subunits. The ketone functionality of the guest molecule (CPK model, red) participates in the structural seam at each end of the capsule through bifurcated hydrogen bonds. Find out more about encapsulating complexes in the review by Rebek, Jr., et al. on p. 1488 ff.

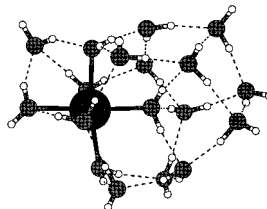


REVIEWS

Contents

Cluster structures, predictably unpredictable?

Theoretical determination of cluster structures is difficult for various reasons. Problems are posed not only by the size of the cluster and the extremely large number of local energy minima induced by its size, but also by the discontinuous dependence of basic structural principles on size, which is noticed empirically again and again. This situation can lead to structures that are intuitively hard to understand, for example, in the case of microhydration clusters of the sodium cation (see picture). An exemplary overview of current work demonstrates that we are still far away from a basic understanding of these structural transitions.



B. Hartke * 1468–1487

Structural Transitions in Clusters

Keywords: aggregation • cluster compounds • global optimization • magic numbers • structure elucidation

Angew. Chem. **2002**, *114*, 1534–1554

The medium is the message: Molecules encapsulated within noncovalent host frameworks (see picture) are reversibly isolated from the influence of solvent molecules and other reagents at room temperature and in solution. These complexes give rise to a wide variety of emergent properties including chiral selection, transduction of optical signals, polymerization, catalysis, and the stabilization of reactive species.

Angew. Chem. **2002**, *114*, 1556–1578



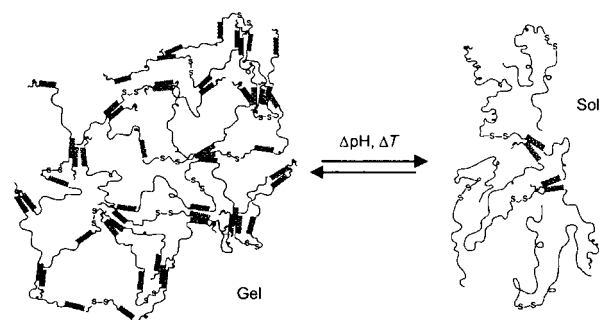
F. Hof, S. L. Craig, C. Nuckolls,
J. Rebek, Jr. * 1488–1508

Molecular Encapsulation

Keywords: host–guest systems •
molecular capsules • molecular
recognition • self-assembly

HIGHLIGHTS

Absolute uniform chain lengths and amino acid sequences as well as well-defined folding patterns that determine structure and properties characterize natural proteins. Advances in chemical and biological peptide synthesis allow improved control over the composition and structure of artificial proteins and peptide hybrid materials, which opens up pathways for the development of new protein-inspired materials, for example, reversible protein hydrogels (see scheme).



Angew. Chem. **2002**, *114*, 1579–1583

H.-A. Klok * 1509–1513

Protein-Inspired Materials: Synthetic
Concepts and Potential Applications

Keywords: biosynthesis • peptides •
proteins • ring-opening polymerization •
solid-phase 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>

Synthesis and Structure of Na_3N

D. Fischer, M. Jansen*



Synthesis and Characterization of a Digermanium Analogue of an Alkyne

M. Stender, A. D. Phillips,
R. J. Wright, P. P. Power*



A Short Synthesis of (+)-13-Deoxyserratine

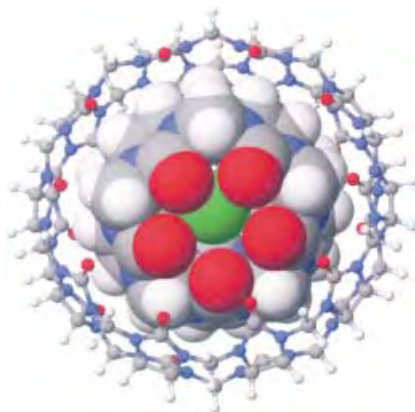
J. Cassayre, F. Gagosz,
S. Z. Zard*



Catalytic Activity and Poisoning of Specific Sites on Supported Metal Nanoparticles

J. Hoffmann, V. Johánek,
J. Hartmann, J. Libuda,*
H.-J. Freund

A spinner in a cage, or put simply, a gyroscope. A “molecular gyroscope”, known as gyroscane (see picture), was recently synthesized. Often such systems are referred to as molecular machines—why not as molecular toys? In this contribution the author illustrates that this view does not have to have negative connotations.



Angew. Chem. **2002**, *114*, 1583–1586

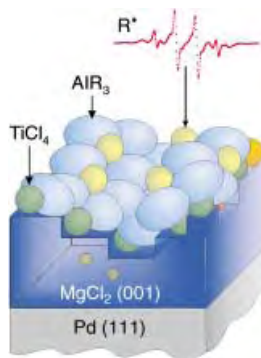
C. A. Schalley* 1513–1515

Of Molecular Gyroscopes, Matroshka Dolls, and Other “Nano”-Toys

Keywords: cucurbituril • host–guest systems • molecular devices • supramolecular chemistry

COMMUNICATIONS

Are radicals involved in the activation of a heterogeneous Ziegler–Natta catalyst? The activation of titanium centers in an active Ziegler–Natta model system initiated by alkyl aluminum compounds has been shown by ESR spectroscopy under ultrahigh-vacuum conditions to proceed, in the case of trimethylaluminum, by a radical mechanism (see picture). In contrast, no indication of radical production is found when the ethyl derivative is used for activation.



Angew. Chem. **2002**, *114*, 1587–1591

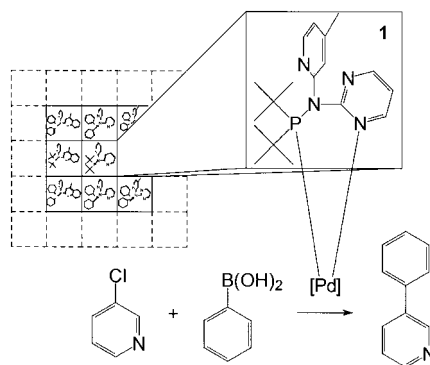
T. Risse,* J. Schmidt, H. Hamann, H.-J. Freund 1517–1520

Direct Observation of Radicals in the Activation of Ziegler–Natta Catalysts

Keywords: EPR spectroscopy • heterogeneous catalysis • surface chemistry • Ziegler–Natta catalysts



The parallel synthesis of homogeneous catalysts is successful with ligands such as **1**. They coordinate metals of Group 10 with the formation of a five-membered chelate ring (see scheme). The resulting metal complexes are efficient catalysts which can activate C(aryl)–chloro bonds and can, for example, mediate the Suzuki coupling of 3-chloropyridine with phenylboronic acid to form 3-phenylpyridine.



Angew. Chem. **2002**, *114*, 1591–1594

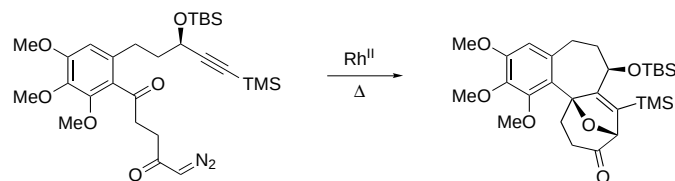
T. Schareina, R. Kempe* ... 1521–1523

Combinatorial Libraries with P-Functionalized Aminopyridines: Ligands for the Preparation of Efficient C(Aryl)–Cl Activation Catalysts

Keywords: C–C coupling • C–Cl activation • chelates • combinatorial chemistry • N,P ligands



The major alkaloid of the meadow saffron is colchicine, which displays remarkable antimitotic activity and has long been used in the treatment of acute gout and is currently being tested against a broad variety of other diseases. In a remarkable Rh-catalyzed domino transformation, the complete carbon skeleton of this important alkaloid is assembled with high efficiency (see scheme). TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



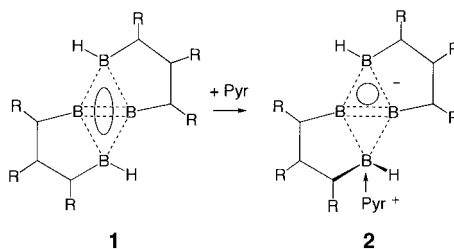
Angew. Chem. **2002**, *114*, 1594–1597

T. Graening, W. Friedrichsen, J. Lex, H.-G. Schmalz* 1524–1526

Facile Construction of the Colchicine Skeleton By a Rhodium-Catalyzed Cyclization/Cycloaddition Cascade

Keywords: alkaloids • cycloaddition • polycycles • rhodium • ylides

The diamond-shaped tetraborane(6) **1** and its pyridine adduct **2** are the first aromatic compounds in which two π electrons display cyclic delocalization over four and three boron centers, respectively (see scheme). The two compounds contain the shortest B–B distances ever observed. R = SiMe₃, Pyr = 4-*tert*-butylpyridine.



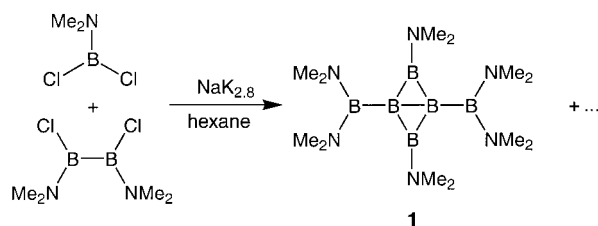
C. Präsang, M. Hofmann, G. Geiseler, W. Massa, A. Berndt * 1526–1529

Aromatic Boranes with Planar-Tetracoordinate Boron Atoms and Very Short B–B Distances

Keywords: aromaticity • boron • density functional calculations • electronic structure • multicenter bonds

Angew. Chem. **2002**, *114*, 1597–1599

The reduction of dimethylaminodichloroborane and dimethylaminodichlorodiborane(4) with NaK_{2.8} alloy provides the new tetraborane(4) **1** (see scheme). The unusual bonding situation in **1** is explained on the basis of molecular-orbital calculations.



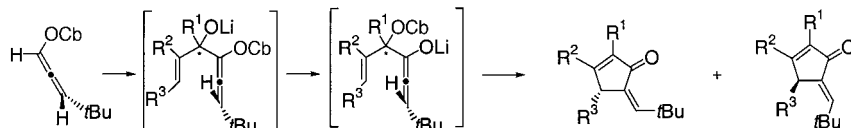
A. Maier, M. Hofmann, H. Pritzkow, W. Siebert * 1529–1532

A Planar, Aromatic *bicyclo*-Tetraborane(4)

Keywords: aromaticity • boron • density functional calculations • electronic structure • multicenter bonds

Angew. Chem. **2002**, *114*, 1600–1602

A stereospecific ring-closure reaction takes place between chiral allenyl carbamates and enones. After lithiation, carbonyl addition, and subsequent carbamoyl (Cb = CONiPr₂) group migration (see scheme), a stereospecific conrotatory cyclization leads to 5-alkylidene-2-cyclopentenones.



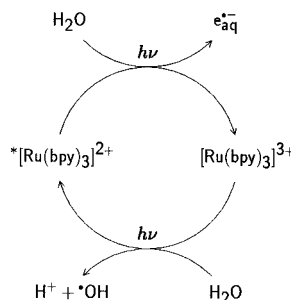
C. Schultz-Fademrecht, M. A. Tius,* S. Grimme,* B. Wibbeling, D. Hoppe * 1532–1535

Synthesis of Enantioenriched 5-Alkylidene-2-cyclopentenones from Chiral Allenyl Carbamates: Generation of a Chiral Lithium Allenolate and Allylic Activation for a Conrotatory 4 π -Electrocyclization

Keywords: allenes • asymmetric synthesis • chirality transfer • cyclization • cyclopentenones

Angew. Chem. **2002**, *114*, 1610–1612

In spite of its model character, the mechanism of the photoionization described here has received very little attention. It is demonstrated that the electronically excited species $^*[\text{Ru}(\text{bpy})_3]^{2+}$ acts as a catalyst, and is regenerated in its excited state by a photoreaction of the ionized ruthenium complex $[\text{Ru}(\text{bpy})_3]^{3+}$ with water (see catalytic cycle; bpy = 2,2'-bipyridine).



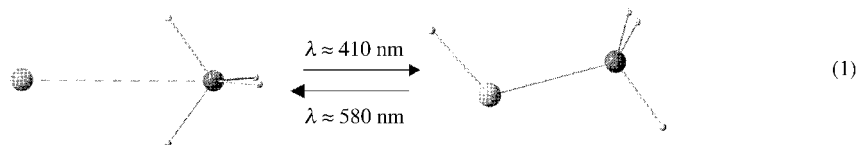
M. Goez,* M. Schiewek, M. H. O. Musa 1535–1538

Near-UV Photoionization of $[\text{Ru}(\text{bpy})_3]^{2+}$: A Catalytic Cycle with an Excited Species as Catalyst

Keywords: kinetics • laser chemistry • photochemistry • ruthenium • solvated electrons

Angew. Chem. **2002**, *114*, 1606–1609

Matrix isolation experiments have enabled the first characterization of the aluminum–silane complex $\text{Al} \cdot \text{SiH}_4$ (η^2 coordination) which can be converted reversibly by selective photolysis into its tautomer HAlSiH_3 [Eq. (1)]. Broadband UV/Vis photolysis causes decomposition of HAlSiH_3 to give the aluminum(I) species AlSiH_3 .



Angew. Chem. **2002**, *114*, 1602–1606

B. Gaertner, H.-J. Himmel* . 1538–1541

Characterization and Photochemistry of the Silane–Aluminum Complex $\text{Al} \cdot \text{SiH}_4$ and Its Photoproducts HAlSiH_3 and AlSiH_3 in a Solid Argon Matrix

Keywords: aluminum • insertion • matrix isolation • photolysis • silane

In situ ultrasmall-angle X-ray scattering (USAXS) on polymer- and protein-mediated silica transformations revealed a phase-separation process in which mesophases direct silica aggregation. The USAXS spectra obtained from the synthesized silica have characteristic features that resemble those observed for pore structures in diatom exoskeletons. The hypothesis that mesophases could explain silica biomineralization in diatoms is discussed.

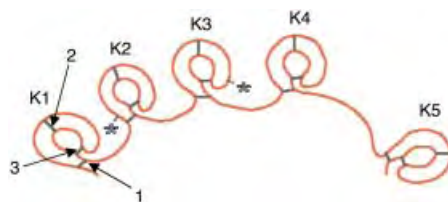
Angew. Chem. **2002**, *114*, 1613–1616

E. G. Vrieling,* T. P. M. Beelen,
R. A. van Santen,
W. W. C. Gieskes* 1543–1546

Mesophases of (Bio)Polymer–Silica Particles Inspire a Model for Silica Biomineralization in Diatoms

Keywords: bioinorganic chemistry • biomineralization • diatoms • silicon • ultrasmall-angle X-ray scattering

The redox environment controls the topology and mechanical properties of angiotensin by modifying the extent of pairing of the three internal disulfide bonds (1–3, see picture) within its five Kringle domains (K1–K5). This situation was revealed by single-molecule force-spectroscopy experiments, analysis of the data, which also allowed the distribution of the different thiol/disulfide reduction intermediates to be estimated.



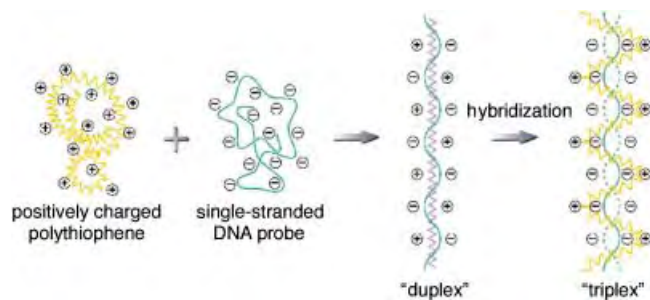
Angew. Chem. **2002**, *114*, 1616–1618

Y. Bustanji, B. Samori* 1546–1548

The Mechanical Properties of Human Angiotensin Can Be Modulated by Means of Its Disulfide Bonds: A Single-Molecule Force-Spectroscopy Study

Keywords: proteins • reduction • scanning probe microscopy • single-molecule studies

 **Different electrostatic interactions** and conformational structures between single- or double-stranded negatively charged nucleic acids bound to a surface (see picture) and water-soluble cationic poly(3-alkoxy-4-methylthiophene) derivatives (in yellow) provide the basis for a sensitive optical detection method (colorimetric or fluorometric) for oligonucleotide hybridization.



Angew. Chem. **2002**, *114*, 1618–1621

H.-A. Ho, M. Boissinot, M. G. Bergeron,
G. Corbeil, K. Doré, D. Boudreau,
M. Leclerc* 1548–1551

Colorimetric and Fluorometric Detection of Nucleic Acids Using Cationic Polythiophene Derivatives

Keywords: conducting materials • DNA recognition • electrostatic interactions • fluorescence • nucleic acids • sensors

A simple yet powerful strategy for the molecular design of chiral phase-transfer catalysts: Conformationally flexible, *N*-spiro chiral quaternary ammonium bromides of type **1** have been newly designed and are found to exert high chiral efficiency by taking advantage of the considerable difference of activity between the diastereomeric homo- and heterochiral isomers through rapid conformational interconversion.



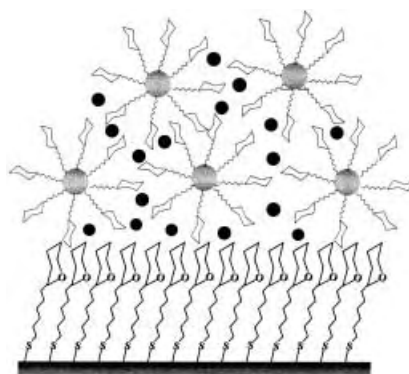
Angew. Chem. **2002**, *114*, 1621–1624

T. Ooi, Y. Uematsu, M. Kameda,
K. Maruoka* 1551–1554

Conformationally Flexible, Chiral
Quaternary Ammonium Bromides for
Asymmetric Phase-Transfer Catalysis

Keywords: alkylation • asymmetric
catalysis • atropinversion •
conformational flexibility • phase-
transfer catalysis

More evidence for carbohydrate self-interactions as a first step in cell adhesion and recognition has been found in experiments with gold glyconanoparticles and self-assembled monolayers presenting carbohydrate epitopes (see picture). The Ca^{2+} -ion-dependent interactions were studied and quantified by surface plasmon resonance. Gray circles = gold nanoparticles, black circles = Ca^{2+} ions.



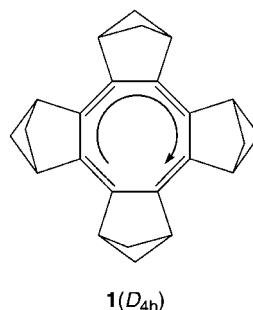
Angew. Chem. **2002**, *114*, 1624–1627

M. J. Hernáiz, J. M. de la Fuente,
Á. G. Barrientos,
S. Penadés* 1554–1557

A Model System Mimicking
Glycosphingolipid Clusters to Quantify
Carbohydrate Self-Interactions by
Surface Plasmon Resonance

Keywords: carbohydrates • glycolipids •
noncovalent interactions • self-assembly •
surface plasmon resonance

Despite considerable bond alternation, the planar cyclooctatetraene (COT) moiety in tetrakis(bicyclo[2.1.1]hexeno)cyclooctatetraene (**1**(D_{4h})) sustains a strong central paratropic ring current, as expected of an antiaromatic monocycle. The paratropic ring current of the COT moiety can be switched on or off by tuning the rotationally allowed COT HOMO–LUMO transition, for example, by choosing saturated or unsaturated clamps.



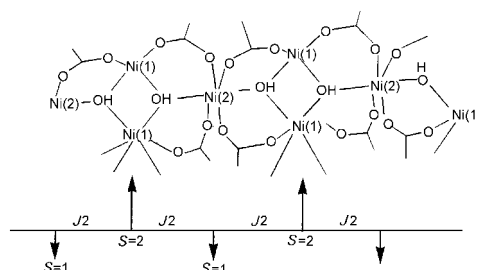
Angew. Chem. **2002**, *114*, 1628–1630

P. W. Fowler, R. W. A. Havenith,
L. W. Jenneskens,* A. Soncini,
E. Steiner 1558–1560

Paratropic Delocalized Ring Currents in
Flattened Cyclooctatetraene Systems with
Bond Alternation

Keywords: ab initio calculations •
annulenes • aromaticity • NMR
spectroscopy • ring currents

Chains of fused Ni^{II} octahedral units form a 3D network and thereby the first example of a homometallic 3D ferrimagnet. The material was characterized by X-ray analysis and a low-temperature magnetic study. The structure features an infinite $-\text{Ni}-(\mu_3\text{-OH})-\text{Ni}_2-$ chain and the spin of adjacent Ni centers alternates between $S=1$ and $S=2$ (see picture).



Angew. Chem. **2002**, *114*, 1631–1633

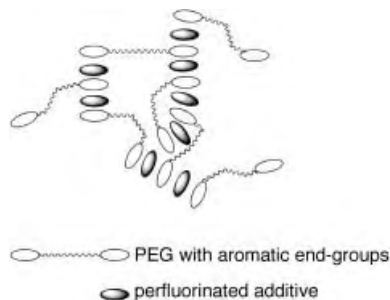
S. Konar, P. S. Mukherjee, E. Zangrando,
F. Lloret,* N. R. Chaudhuri* 1561–1563

A Three-Dimensional Homometallic
Molecular Ferrimagnet

Keywords: coordination chemistry •
ferrimagnetism • magnetic properties •
nickel • O ligands



Stiff PEGs: Aqueous solutions of pyrene end-capped poly(ethylene glycol)s (PEGs) increase their viscosity in the presence of octafluoronaphthalene possibly as a result of aggregation by face-to-face stacking (shown schematically). The exploitation of the arene–perfluoroarene supramolecular synthon in solution is reported.



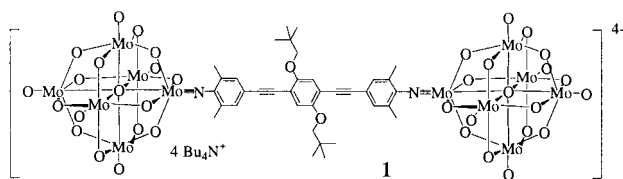
Angew. Chem. **2002**, *114*, 1633–1636

A. F. M. Kilbinger,
R. H. Grubbs* 1563–1566

Arene–Perfluoroarene Interactions as
Physical Cross-Links for Hydrogel
Formation

Keywords: aggregation • gels •
noncovalent interactions • polymers •
stacking interactions

Strong electronic interactions occur between the polyoxometalate (POM) clusters and the π electrons of the conjugated organic bridge in hybrid molecular dumbbells such as **1** which were synthesized by Pd-catalyzed coupling reactions of organoimido-substituted POMs.



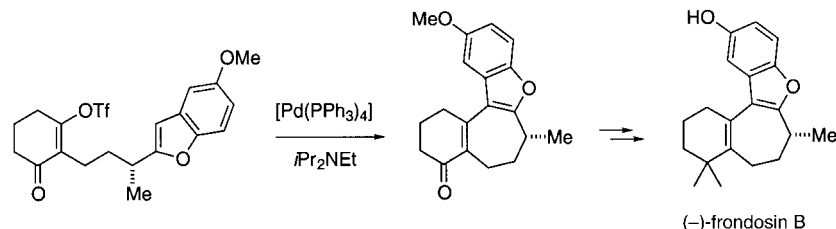
Angew. Chem. **2002**, *114*, 1636–1638

M. Lu, Y. Wei, B. Xu, C. F.-C. Cheung,
Z. Peng,* D. R. Powell 1566–1568

Hybrid Molecular Dumbbells: Bridging
Polyoxometalate Clusters with an Organic
 π -Conjugated Rod

Keywords: C–C coupling •
molybdenum • organic–inorganic hybrid
composites • palladium •
polyoxometalates

Sidestepping stereochemical inversion: In an expedient, asymmetric total synthesis of (–)-frondosin B a novel palladium-catalyzed cyclization establishes the tetracyclic skeleton (see scheme). The absolute stereochemistry of naturally occurring marine metabolite (+)-frondosin B, an interleukin-8 inhibitor, has been reassigned. Tf = trifluoromethanesulfonyl.



Angew. Chem. **2002**, *114*, 1639–1642

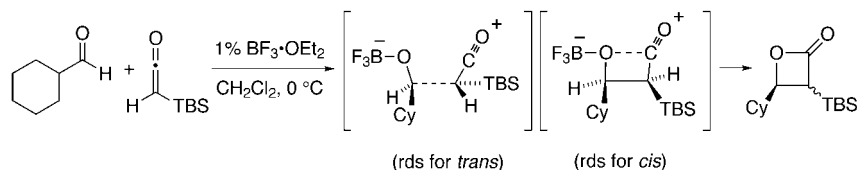
C. C. Hughes, D. Trauner* .. 1569–1572

Concise Total Synthesis of
(–)-Frondosin B Using a Novel
Palladium-Catalyzed Cyclization

Keywords: cyclization • natural
products • palladium • polycycles •
total synthesis



Divergent rate-limiting steps for the formation of diastereomeric products! Evidence for this unexpected finding comes from experimental and theoretical studies of the title reaction. The predicted differing rate-determining steps (rds) in the formation of *cis*- and *trans*- β -lactones (see scheme; cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl) are used to explain the stereoselectivity of these reactions and suggest that a broader range of mechanistic possibilities should sometimes be considered in reactions leading to diastereomeric products.



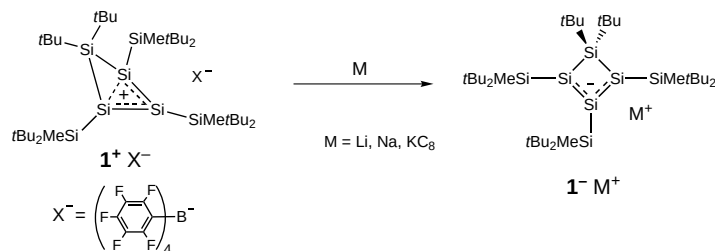
Angew. Chem. **2002**, *114*, 1642–1645

D. A. Singleton,* Y. Wang, H. W. Yang,
D. Romo* 1572–1575

Mechanism and Origin of
Stereoselectivity in Lewis Acid Catalyzed
[2 + 2] Cycloadditions of Ketenes with
Aldehydes

Keywords: ab initio calculations •
cycloaddition • isotope effects •
ketenes • lactones

Alkali-metal derivatives of cyclotetrasilene (1^-) were obtained by the treatment of cyclotetrasilenylium ion (1^+) or cyclotetrasilenyl radical ($1^\bullet$) with Li, Na, and KC_8 in diethyl ether. X-ray crystallographic analysis of $1^- Li^+$ suggests that it has a cyclotetrasilene structure with a Si=Si bond in the ring, and that the lithium cation interacts with the three silicon atoms in the four-membered-ring skeleton. The ion 1^- is readily oxidized to $1^\bullet$ and 1^+ ; this is a reversible chemical redox system.



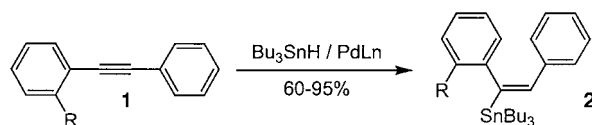
Angew. Chem. **2002**, *114*, 1645–1647

T. Matsuno, M. Ichinohe,
A. Sekiguchi* 1575–1577

Cyclotetrasilene Anion: A Reversible
Redox System of Cyclotetrasilenylium
Cation, Radical, and Anion

Keywords: alkali metals • lithium • redox
chemistry • silicon • small-ring systems

An unprecedented ortho-directing effect (ODE) in diaryl alkynes **1** (R = electron-withdrawing or electron-donating group) promotes regioselective addition of tributyltin hydride to the triple bond and afforded efficiently stannylated unsymmetrical 1,2-diaryl olefins **2**. The precise contributions of steric, electronic, and coordinative factors, which control this regioselectivity are highlighted. The results are rationalized in terms of electronic polarization across the alkyne bond, induced by the *ortho* substituent whatever its electronic nature.



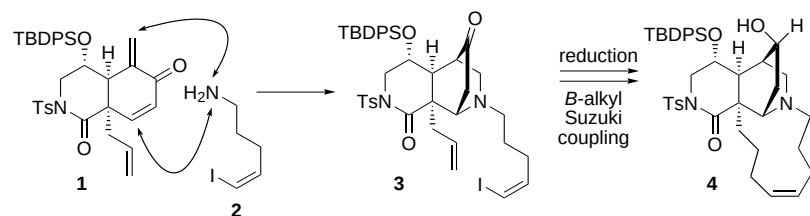
Angew. Chem. **2002**, *114*, 1648–1650

M. Alami,* F. Liron, M. Gervais,
J.-F. Peyrat, J.-D. Brion 1578–1580

Ortho Substituents Direct Regioselective
Addition of Tributyltin Hydride to
Unsymmetrical Diaryl (or Heteroaryl)
Alkynes: An Efficient Route to
Stannylated Stilbene Derivatives

Keywords: alkenes • alkynes •
hydrostannation • palladium • tin

A double Michael addition of amine **2** to **1** was a key reaction in the synthesis of the isoquinuclidine core **4** of xestocyclamine A, a protein kinase C inhibitor. The first ansa bridge was formed efficiently by a *B*-alkyl Suzuki coupling in **3**. TBDPS = *tert*-butyldiphenylsilyl; Ts = *p*-toluenesulfonyl.



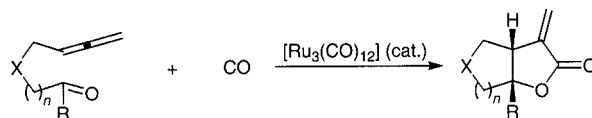
Angew. Chem. **2002**, *114*, 1651–1654

A. Gagnon,
S. J. Danishefsky* 1581–1584

Evaluation of Diene Hierarchies for
Diels–Alder Reactions En Route to
Xestocyclamine A: Elaboration of an
Ansa Bridge by *B*-Alkyl Suzuki
Macrocyclization

Keywords: alkaloids • annulation • cross-
coupling • cycloaddition • macrocycles

An efficient route to α -methylene- γ -lactones involves the Ru-catalyzed [2+2+1] cycloadditions of allenyl aldehydes and ketones with CO (see scheme; $n = 1, 2$; R = H, CH_3 ; X = NTs, O, $C(CO_2Et)_2$; Ts = toluene-4-sulfonyl). The α -methylene- γ -lactone moiety is found in numerous biologically active natural products.



Angew. Chem. **2002**, *114*, 1654–1656

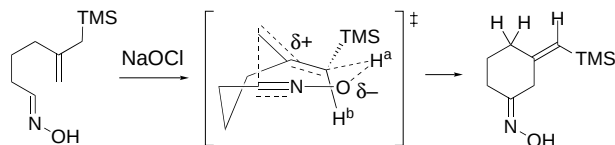
S.-K. Kang,* K.-J. Kim,
Y.-T. Hong 1584–1586

Synthesis of α -Methylene- γ -
butyrolactones: Ru-Catalyzed
Cyclocarbonylation of Allenyl Aldehydes
and Allenyl Ketones

Keywords: aldehydes • allenes •
cycloaddition • ketones • lactones •
ruthenium



“I took the road less traveled by and that has made all the difference.” Not only fans of the poet Robert Frost recognize the attraction of the less common reaction path. Rather than the expected [3+2] cycloaddition, a novel ene-like cycloisomerization occurs on deprotonation of allyltrimethylsilyl–oxime compounds when the β -sp² carbon atom of the allyltrimethylsilyl moiety is tethered to the oxime unit (see scheme). The resulting nitrile oxide functional group serves as an enophile, and the final cyclized product still has two functional groups suitable for further manipulations. TMS = SiMe₃.



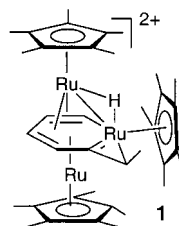
Angew. Chem. **2002**, *114*, 1656–1658

T. Ishikawa,* J. Urano, S. Ikeda,
Y. Kobayashi, S. Saito* 1586–1588

Novel Ene-Like Cycloisomerization
Reaction of Nitrile Oxides with a
Tethered Allyltrimethylsilyl Group

Keywords: cycloisomerization • nitrile
oxides • oximes • synthetic methods

Although their existence was suggested eight years ago, triple-decker complexes with a central metallabenzene have not been synthesized before. The ruthenabenzene-bridged complex **1** appears to be the first well-characterized example of a complex of this type with a bridging metallabenzene. The unusual central ligand was formed from coordinated norbornadiene via vinylcyclopentadiene.



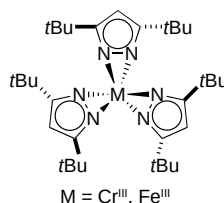
Angew. Chem. **2002**, *114*, 1659–1661

S. H. Liu, W. S. Ng, H. S. Chu, T. B. Wen,
H. Xia, Z. Y. Zhou, C. P. Lau,
G. Jia* 1589–1591

A Triple-Decker Complex with a Central
Metallabenzene

Keywords: C–C activation • coordination
chemistry • metallacycles • ruthenium •
sandwich complexes

η^2 coordination of pyrazolato ligands is currently unknown for d-block metal complexes with d² or higher electronic configurations, and all known Group 6–11 metal–pyrazolato complexes contain η^1 , μ : η^1 , η^1 , or η^5 ligands. Tris(3,5-di-*tert*-butylpyrazolato)chromium(III) and tris(3,5-di-*tert*-butylpyrazolato)iron(III) (see picture), which contain η^2 -pyrazolato ligands, have been synthesized, and molecular-orbital calculations indicate that η^2 -pyrazolato coordination is less stable than η^1 coordination in a model iron(III) complex.



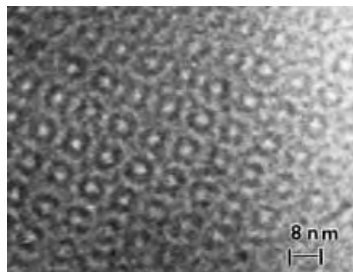
Angew. Chem. **2002**, *114*, 1661–1664

K. R. Gust, J. E. Knox, M. J. Heeg,
H. B. Schlegel,
C. H. Winter* 1591–1594

Synthesis, Structure, and Molecular
Orbital Calculations of Chromium(III) and
Iron(III) Complexes Containing
 η^2 -Pyrazolato Ligands

Keywords: ab initio calculations •
chromium • iron • ligand design •
N ligands

Acidic pores: The first cubic mesoporous tin(IV) phosphate and its hexagonal form are reported and characterized by X-ray diffraction, transmission electron microscopy (see picture of the cubic domain), and Brunauer–Emmet–Teller techniques. Microcalorimetric experiments and preliminary catalytic tests indicate that these solids are very acidic and exhibit a good catalytic activity for the removal of NO_x (deNO_x).



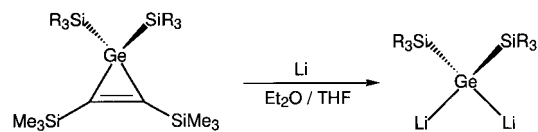
Angew. Chem. **2002**, *114*, 1664–1667

C. Serre,* A. Auroux, A. Gervasini,
M. Hervieu, G. Férey 1594–1597

Hexagonal and Cubic Thermally Stable
Mesoporous Tin(IV) Phosphates with
Acidic and Catalytic Properties

Keywords: heterogeneous catalysis •
mesoporous materials •
microcalorimetry • nitrogen oxides •
phosphates • tin

1,1-Dilithiogermaenes 1a and 1b were obtained by treatment of the persilyl-substituted germacycloprenes with lithium, which cleaved the two Ge–C bonds in the three-membered ring. The structure of **1b** has been confirmed by X-ray crystallography and shows a dimeric structure with a rather unusual arrangement of the two Li atoms. The use of **1** in the effective preparation of double-bonded derivatives of heavier Group 14 elements has also been shown.



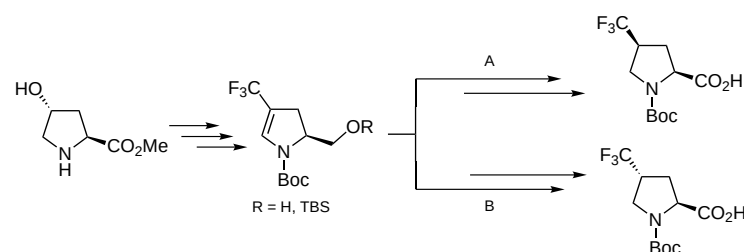
a: $R_3 = tPr_3$, **b:** $R_3 = tBu_2Me$

1

Angew. Chem. **2002**, *114*, 1668–1670



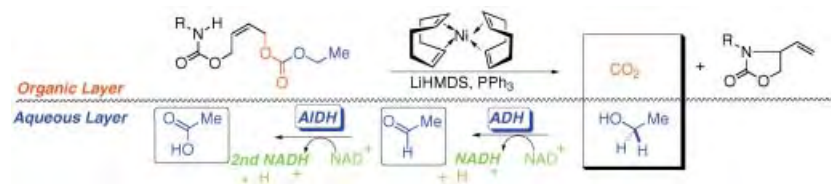
Stereocontrolled synthesis of *cis* and *trans*-substituted prolines by a divergent approach, leads to the preparation of *cis*-(4*S*)- and *trans*-(4*R*)-trifluoromethyl-L-proline from hydroxyproline. The key pyrroline intermediates were subjected to hydrogenation (see scheme; A = sterically directed hydrogenation, B = hydroxy-directed hydrogenation; Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl), to afford products in high diastereomeric excess.



Angew. Chem. **2002**, *114*, 1670–1672



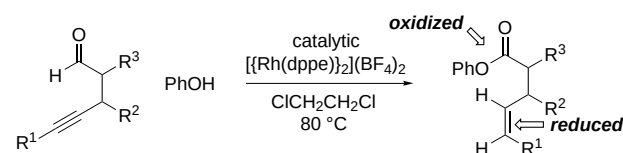
Can enzymes help organic chemists identify new transition-metal catalysts? The first example of the *in situ* enzymatic monitoring of an organic transformation is described. Thus, a transition-metal-mediated allylic-amination reaction in the organic layer (see scheme; R = *para*-methoxyphenyl, tosyl) leads to release of ethanol which causes the spectroscopically observable formation of NADH in the aqueous phase. This approach uncovers a new Ni^0 -promoted route to β,γ -unsaturated amino acids. HMDS = 1,1,1,3,3,3-hexamethyldisilazane.



Angew. Chem. **2002**, *114*, 1673–1677



Two complementary transformations in one go: A rhodium-catalyzed transformation has been developed in which a phenol reacts with a 4-alkynal to furnish a *cis*-4-alkenoate in good yield (see scheme; dppe = 1,2-bis(diphenylphosphino)ethane). This novel tandem process couples the reduction of an alkyne to an alkene with the oxidation of an aldehyde to an ester.



Angew. Chem. **2002**, *114*, 1677–1679

A. Sekiguchi,* R. Izumi, S. Ihara,
M. Ichinohe, V. Y. Lee 1598–1600

The First Isolable 1,1-Dilithiogermaene and Its Unusual Dimeric Structure—An Effective Reagent for the Preparation of Double-Bonded Derivatives of Group 14 Elements

Keywords: alkali metals • germanium • lithium • reduction • small ring systems

J. R. Del Valle,
M. Goodman* 1600–1602

Stereoselective Synthesis of Boc-Protected *cis* and *trans*-4-Trifluoromethylprolines by Asymmetric Hydrogenation Reactions

Keywords: amino acids • diastereoselectivity • hydrogenation • peptidomimetics • trifluoromethylation

D. B. Berkowitz,* M. Bose,
S. Choi 1603–1607

In Situ Enzymatic Screening (ISES): A Tool for Catalyst Discovery and Reaction Development

Keywords: allylic substitution • amino acids • catalyst screening • enzymes • nickel • transition metals

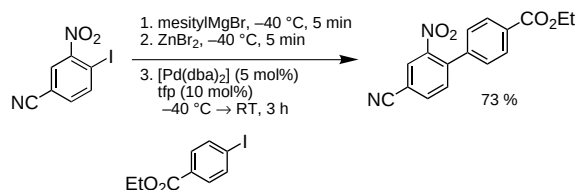
K. Tanaka, G. C. Fu* 1607–1609

A Novel Rhodium-Catalyzed Reduction–Oxidation Process: Reaction of 4-Alkynals with Phenol to Provide *cis*-4-Alkenoates

Keywords: alkynes • homogeneous catalysis • oxidation • reduction • rhodium



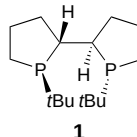
Highly functionalized aryl Grignard reagents with an *ortho*-nitro substituent have been synthesized from 2-iodonitroaryl compounds through an I–Mg exchange reaction with PhMgCl or mesityl magnesium bromide (see scheme). These reagents are stable ($T < -20^\circ\text{C}$ for several hours) and undergo various cross-coupling reactions in the presence of Cu or Pd catalysts (dba = *trans,trans*-dibenzylideneacetone; tfp = tri-*o*-furylphosphane).



Angew. Chem. **2002**, *114*, 1680–1681



TangPhos (1) is a highly efficient and practical ligand for asymmetric hydrogenations. High enantioselectivities and turnover numbers were observed in the Rh-catalyzed hydrogenation of α -(acylamino)acrylic acids and α -arylenamides.



Keywords: cross-coupling • Grignard reaction • halogen–magnesium exchange • iodine • nitro group

W. Tang, X. Zhang* 1612–1614

A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations

Keywords: asymmetric catalysis • enamides • hydrogenation • P ligands • rhodium

M. Reggelin,* M. Schultz, M. Holbach 1614–1617

Helical Chiral Polymers without Additional Stereogenic Units: A New Class of Ligands in Asymmetric Catalysis

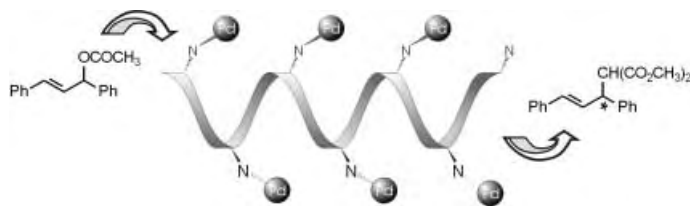
Keywords: allylic substitutions • asymmetric catalysis • chirality • helical structures • polymers

* Author to whom correspondence should be addressed

Angew. Chem. **2002**, *114*, 1682–1684



No other sources of chirality except its helicity are present in the polymeric ligand shown, which was prepared by helix-sense-selective polymerization. Palladium complexes of this ligand catalyze allylic substitution reactions. The resulting asymmetric induction is a direct and sole consequence of the uniform helicity of the polymeric ligand.



Angew. Chem. **2002**, *114*, 1684–1687



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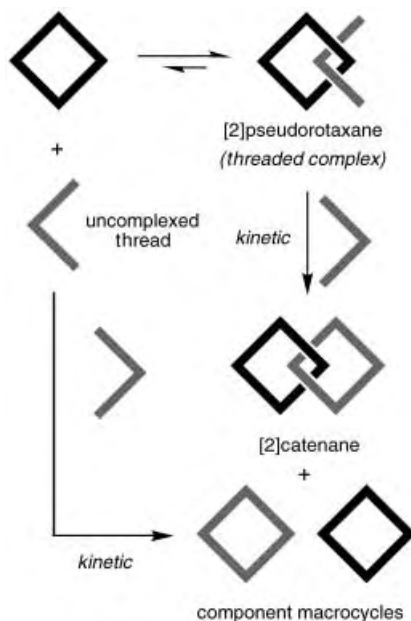
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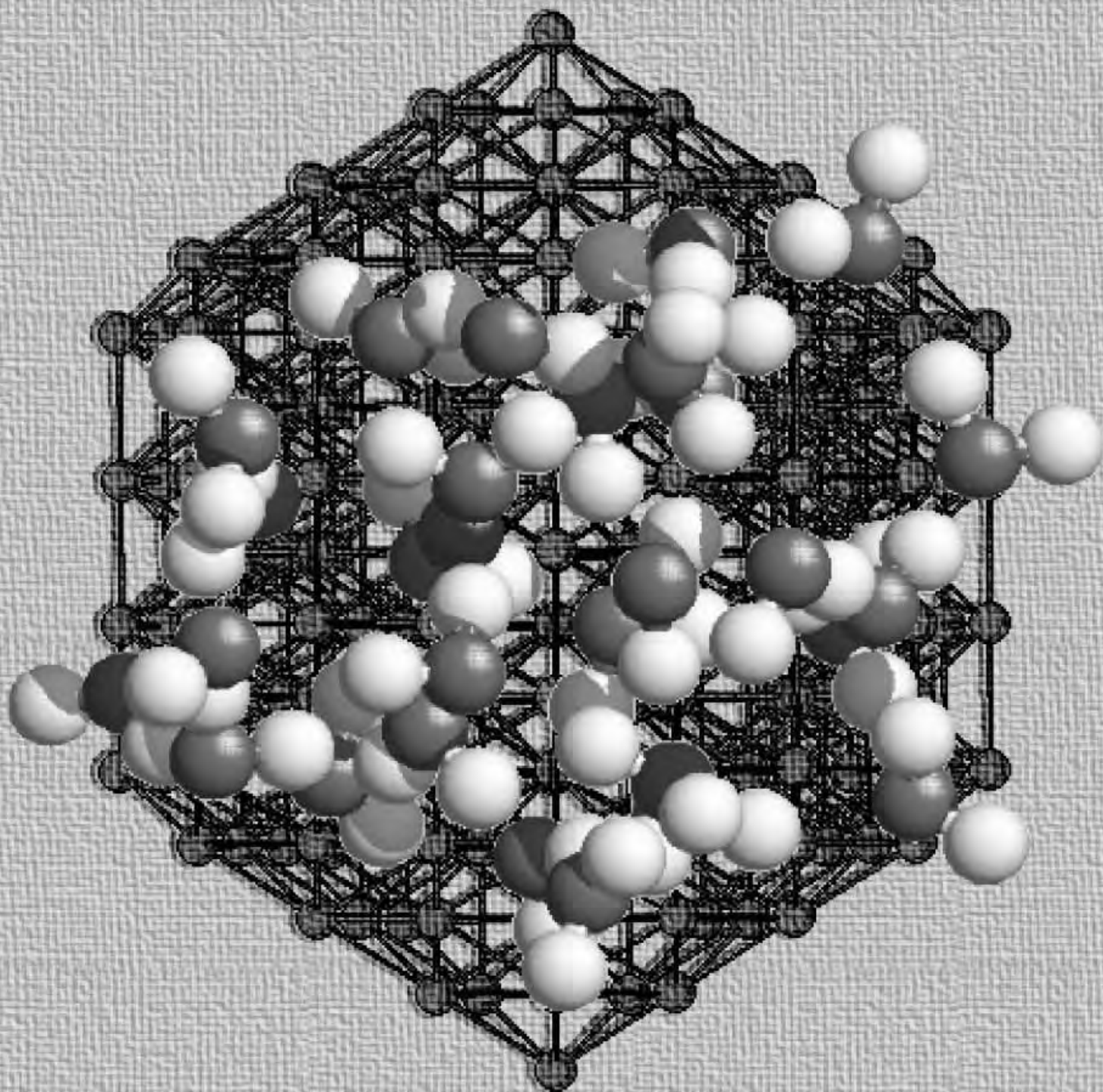
CORRIGENDA

In the Communication by **A. Plückthun and G. M. Blackburn et al.** in Issue 5, **2002**, pp. 775–777 a footnote was not included, which points out that the authors J. R. Betley and S. Cesaro-Tadic contributed equally to this work. The editors apologize for the error.

In the Review by **S. J. Rowan et al.** in Issue 6, **2002**, pp. 898–952, an error was inadvertently introduced into Scheme 49 during the printing process. The correct scheme is shown below. The editorial team apologizes for this error.



What do noble-gas clusters (background) and
apparently amorphous water clusters
(foreground) have in common?
Their structures change with cluster size.



Structural Transitions in Clusters**

Bernd Hartke*

If one adds more particles to a cluster, the energetically optimal structure is neither preserved nor does it change in a continuous fashion. Instead, one finds several cluster size regions where one structural principle dominates almost without exception, and rather narrow boundary regions in-between. The structure of the solid is usually reached only at relatively large sizes, after more than one structural transition. The occurrence of this general phenomenon of size-dependent structural transitions does not seem to depend on the nature of the particles, it is found for atomic, molecular,

homogeneous, and heterogeneous clusters alike. Clearly, it is a collective many-body phenomenon which can in principle be calculated but not understood in a fully reductionistic manner. Actual calculations with sufficient accuracy are not feasible today, because of the enormous computational expense, even when unconventional evolutionary algorithms are employed for global geometry optimization. Therefore, simple rules for cluster structures are highly desirable. In fact, we are dealing here not just with the academic quest for linkages between cluster structure and features of the potential

energy surface, but structural transitions in clusters are also of immediate relevance for many natural and industrial processes, ranging from crystal growth all the way to nanotechnology. This article provides an exemplary overview of research on this topic, from simple model systems where first qualitative explanations start to be successful, up to more realistic complex systems which are still beyond our understanding.

Keywords: aggregation • cluster compounds • global optimization • magic numbers • structure elucidation

1. Introduction

1.1. Importance of Clusters

In the present article, we are not interested in the clusters of inorganic or organometallic chemistry,^[1, 2] with comparatively few (transition) (metal) atoms next to each other, surrounded by numerous ligands and (possibly complicated) counterions, needed to make the formation and stability of these clusters possible. We are also not interested in ligand-covered nanoparticles,^[3, 4] now generated and examined in many experiments and by some theoreticians. Instead, our focus is on “naked” clusters, with, as experimental reference, the molecular beams used by physical chemists or molecular physicists.

Nevertheless, these clusters are by no means elusive curiosities of the laboratory. They are of prime importance in many industrial and natural processes, for example in chemical vapor deposition (CVD)^[6] or in all variants of

nanotechnology,^[7–10] but also in the wide area of aerosols. There, many current studies investigate mixed clusters of ice and sulfuric acid, and their role in ozone depletion in polar stratospheric clouds.^[11]

From the viewpoint of basic theoretical research, clusters form the link between the thoroughly investigated and hence largely well understood world of single molecules and the world of the “infinitely extended” condensed phase, which is also quite accessible with the special methods of this area. This basic interest in clusters culminates in several fundamental questions, for example: at which minimum size does a cluster start to exhibit metallic properties?^[12, 13] In Section 1.2, we argue that even this primary issue of cluster structure is still largely unresolved.

While theoretical treatments of single molecules and also of the periodic solid state are almost routine today, the intermediate region of clusters still constitutes a challenge, for several reasons: These clusters are definitely too large for ab initio calculations, including sophisticated treatments of electron correlation, but empirical potentials often are not sufficiently accurate. The scaling of computational expense with system size still is a problem, in spite of the latest developments in linear scaling ab initio theories;^[14] even the more elaborated empirical potentials can be too expensive for large clusters. And even without using modern catchwords

[*] Prof. Dr. B. Hartke
Institut für Physikalische Chemie
Christian Albrechts Universität
Olsenhausenstrasse 40, 24098 Kiel (Germany)
Fax: (+49)431-880-1758
E-mail: hartke@phc.uni-kiel.de

[**] The abbreviations used in this article are listed in Table 1.

such as complexity and emergent phenomena, we will conclude in Section 2.2 that investigations of clusters need new theoretical principles and techniques.

1.2. Structure of Clusters

The reason that clusters are called clusters and are not simply called molecules is mainly because we do not yet know any simple rules for their structure. The historical hypothesis that clusters are simply pieces of the corresponding solid was disproved very early on.^[15]

Today the opposite proposition is commonly accepted: in general, the structure of small clusters is quite different from that of the “infinitely extended” solid, often even with (local) symmetry elements not allowed in periodic crystals, such as fivefold rotation axes. Unfortunately, this is a negative statement, not leading to any construction principle for clusters. However, a simple argument in favor of this updated proposition does contain at least one possible construction scheme.

It is tempting to ascribe the structural differences between clusters and the solid state to the dominance of surface effects, but this is rather vague and unconstructive; in fact, attempts in this direction can even be misleading, for example in attempts to understand the structures of silicon clusters.^[16, 17] Instead, we want to recall an argument that has been present in the literature for a long time (see Nelson and Spaepen^[18] and the historical references listed there): Imagine a species of atoms interacting like hard spheres or by a somewhat more realistic pair potential (such as the Lennard–Jones (LJ) potential, see Section 3.1; all the abbreviations used are given in Table 1). Arranging these atoms in three dimensions, one can retain optimal packing up to a tetrahedron of four atoms, by maximizing the number of direct contacts or of the number of atom pairs at optimal pair distance. Adding more atoms, it seems to be possible to remain in this state of optimal packing, by generating further tetrahedra. While something like this is actually possible in two dimensions, three-dimensional space cannot be filled with tetrahedra. As shown in Figure 1, suitable arrangements of tetrahedra lead almost to a pentag-

Table 1. Summary of the abbreviations in this article and the section in which they are first used.

Abbreviation	Definition	Section
CCSD(T)	coupled cluster (method including all) single and double (excitations including the) triple (excitations from perturbation theory)	3.4
CPMD	Car–Parrinello MD	2.1
DC	differential convex	2.2.2
DFT	density functional theory	2.1
EA	evolutionary algorithm	2.2.2
fcc	face-centered cubic	3.1
GA	genetic algorithm	2.2.2
GVB	general valence bond theory	2.2.3
hcp	hexagonal close packed	3.1
HF	Hartree–Fock	3.5
LJ	Lennard–Jones	1.2
MC	Monte Carlo	2.1
MD	molecular dynamics	2.1
(L)MP2	(Local) Møller–Plesset perturbation theory 2nd order	3.5
NP	nondeterminist polynomial	2.2.2
OPLS	Optimized potentials for liquid simulations	3.6
QCISD	quadratic configuration interaction (limited to) single (and) double (excitations)	3.3
QMC	quantum Monte Carlo	3.5
rcp	random close packed	3.1
SA	simulated annealing	2.2.2
SCF	self consistent field	2.2.3
TB	tight binding	3.3
TIP4P	transferable intermolecular potential with 4 points	3.5
TTM2-F(R)	Thole-type model 2, flexible (rigid)	3.5
TTP	tetracapped trigonal prism	3.3

onal bipyramid and then almost to an icosahedron—but not exactly. According to the preferred terminology, there remains a gap, the system is “frustrated”, or it becomes impossible to have all nearest neighbors at the optimal pair distance. Figure 1 also depicts the two possibilities of arranging the deviations from optimal pair distances, either in one place, or by distributing them evenly across the cluster. As mentioned below in Section 3.1, these deviations lead to the concept of “strain” in a cluster and to a first qualitative explanation for some structural transitions.



Bernd Hartke, born 1963 in Concepción (Chile), studied chemistry at the University of Würzburg (Germany). After his diploma in 1988, he obtained his Ph.D. in 1990 with a thesis on quantum-mechanical wavepacket dynamics under the supervision of Professor Jörn Manz. For the following two years, he worked on implementations of direct ab initio molecular dynamics as a Liebig fellow of the Fonds der Chemischen Industrie with Professor Emily Carter at the University of California, Los Angeles. In 1992, he started working towards his Habilitation in the group of Professor Hans-Joachim Werner, first at the University of Bielefeld and, since 1994, at the University of Stuttgart. During this time, he broadened his research interests towards global geometry optimization of clusters using evolutionary algorithms. He obtained his Habilitation in theoretical chemistry in 1998, with a thesis that also covered time-independent quantum-mechanical reactive scattering. In 2000, he was awarded a Karl-Winnacker scholarship. In 2001, he accepted a position of full professor for theoretical chemistry at the University of Kiel.

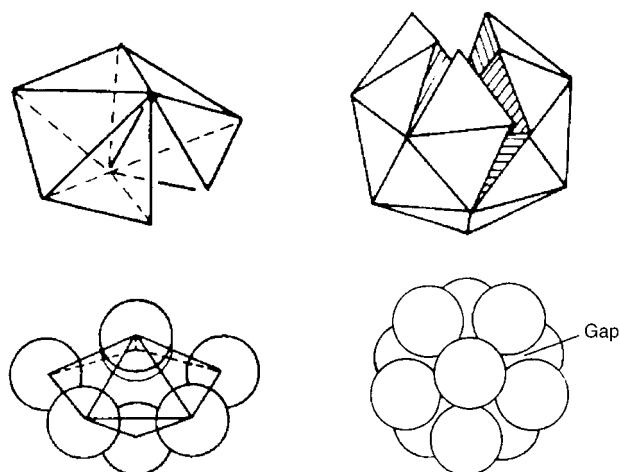


Figure 1. Suitable packing of tetrahedrons in three dimensions almost leads to a pentagonal bipyramid (left column) and to an icosahedron (right column); reproduced with permission from ref. [18].

Restricting ourselves for the moment to particles interacting through such simple pair forces, this line of thought proposes geometries with fivefold rotation axes (the icosahedral structural principle) as a quasi-natural structural scheme for small clusters. In the periodic crystal, however, symmetries of this kind are not allowed. Therefore, even without the problem of frustration, it is not possible to continue packing tetrahedra all the way to the periodic solid state. Hence, upon the successive enlargement of a cluster, there has to be at least one or even several transitions that change of the basic structural principle. (Local polytetrahedral order is indeed possible in extended nonperiodic systems, as in glasses or quasicrystals, which leads to interesting phenomena;^[18] but this is not the main topic of this article.)

If the forces between the particles in the cluster are more complicated, and at least as important as the simple sterical packing argument, further and different basic structures have to be expected for small clusters. However, it should have become clear by now that also in these cases we are likely to see differences between cluster and crystal structures.

Martin et al.^[19, 20] has given a detailed description and analysis of several generic possibilities for packing, together with simple equations relating the number of particles and the number of geometrical shells in the cluster. These ideas can be used to predict and interpret prominent magic numbers as shell closures in these different structural principles, and is important for the interpretation of experiments, but in itself it does not explain the preference of certain packing modes at certain cluster sizes. Searching for explanations for the size dependence of cluster structures and properties, beyond this simple steric packing argument, one frequently meets two models:

1) Physicists like to use the “jellium” model.^[21] When electronic effects dominate, for example, in clusters of alkali metals, it can explain several magic numbers. There is, however, no cluster structure (of ionic cores or atoms) in this model, but only a diffuse, positively charged background or a largely empirical external potential for the electrons. With these assumptions, it is hard to apply this

model to the present problem, where a detailed description of the inner cluster structure is called for, while the outer form remains qualitatively the same.

2) The “liquid-drop” model was developed for extrapolation from larger to smaller clusters. Jortner^[22] gives historical references and explains the model, which is again founded on a simple geometry argument. This model succeeds in reproduction and prediction of smooth trends in large clusters, and provides the basis for the usual plots of properties versus $n^{-1/3}$ (where n is the number of particles in the cluster). It has become common to diagnose magic numbers and transitions as deviations from linearity in such plots. In the last 15 years several authors^[23–25] extended the model with corner and edge contributions, but it still does not take the inner structure of clusters into account. Therefore, it has to fail for the construction of small clusters, where inner structure is important, as was pointed out in the original articles.^[22]

Therefore, as soon as the inner structure of clusters becomes unimportant (because of electronic effects or simply because of cluster size), we are able to interpret and understand (smooth) changes in their properties. But for the interesting region of smaller and nonmetallic clusters (comprising small clusters of metal atoms, and small clusters are always nonmetallic even when they contain metal atoms), which are dominated by the inner structure, basic understanding is still lacking.

According to the simple packing argument (see above), it seems to be clear that there have to be size-dependent structural transitions in clusters, at least for certain classes of potentials (or if certain types of interactions between particles in the cluster dominate). Without expensive calculations (cf. examples in Section 3), nobody can predict the cluster sizes where these transitions occur. That is, we still do not have qualitative and easily understandable connections between the potential energy surface and these transitions; they still have the status of typical “emergent phenomena” of many-particle systems.

It is also still largely unknown how such a transition actually occurs, with the successive addition of particles. It is hard to imagine a gradual transition from one structural principle to a new one, since it can be expected that mixed or partially disordered structures have much higher energies (see, however, ref. [26] for a model comprising several structures). And it is equally hard to imagine a sudden change of the whole cluster structure upon addition of just one more particle. In fact, at sufficiently low temperatures only those clusters can grow into the “correctly” ordered bulk phase that already start their growth within this structure. In this scenario, successful seeds in the collection of small clusters have only locally minimal energy, whereas the globally minimal energy structures turn out to be dead ends for crystal growth. More detailed understanding can only arise from dynamical simulations with atomic resolution at various temperatures, but work of this type is still rare.

In the area of these size-dependent structural transitions of clusters, this article gives an overview of the current state of the art and accentuates the central problems that still need to be solved. It should be emphasized that this problem area is

not just of academic interest. All the questions mentioned above have direct relevance for phenomena such as, crystallization, seed formation and growth, or solid–liquid phase transitions in extended systems.^[27, 28]

These structural transitions should also be compared and contrasted with solid–liquid phase transitions in clusters: the latter occur as a function of temperature, the former as a function of the number of particles. However, transitions between structures that occur with changes in the number of particles have also already been theoretically predicted to occur with temperature changes.^[29] Recently, there has been a surge of interest in temperature-dependent transitions, because now there are not only theoretical studies of phase transitions and coexistence in clusters^[30–33] but also direct experimental observations.^[34] Nevertheless, solid–liquid phase transitions in clusters are not the main topic here.

Similarly, there are analogies and differences between the general problem of cluster structure and the abstract three-dimensional geometrical packing problem: Typical packing problems are formulated with rigid, (periodically) repeated units, and hence are more directly comparable with crystal-structure prediction. In fact, there are now the first connections between abstract geometrical tiling and crystallography.^[35–37] In clusters, however, we are dealing with (to some degree) nonrigid units and with surface effects (or different boundary conditions).

Section 2 briefly introduces and compares several traditional and new theoretical methods for investigating cluster structures, with global geometry optimization by evolutionary algorithms treated in more detail. In Section 3, examples for characteristic structural transitions in various cluster systems are given, with some bias towards the work of our group. The main findings are then summarized in the final Section 4.

2. Theoretical Methods

2.1. Traditional Techniques

To save space, we do not give a comprehensive introduction nor an overview of applications for these techniques. Only the suitability of several methods for our present problem will be discussed.

Molecular dynamics (MD)^[38, 39] and Monte Carlo (MC)^[38, 39] with empirical potentials are long established methods to deal with structure and dynamics of molecules. In recent years, these have been joined by variants that do not need a prefabricated potential energy surface, since this information is generated during the calculation at each current configuration. The most popular one of these is Car–Parrinello MD (CPMD),^[40, 41] where the atoms follow classical trajectories and the forces between them are calculated with density functional theory (DFT) methods. Decisive savings in computer time arise from substituting the costly solution of the quantum chemical eigenvalue problem in a huge basis of plane waves by fictitious dynamics of the wavefunction coefficients, which dynamically adjusts the wavefunction to the movements of the nuclei. Extensions of

this method are direct DFT versions^[42] of the path-integral technique^[43, 44] and direct-DFT versions^[45] of the so-called “centroid MD”,^[46] which allows a quantum mechanical treatment of the nuclear dynamics. Extensions in another direction, going beyond DFT to a full ab initio treatment of the electronic problem, have also been implemented several times.^[47–49] An excellent and detailed comparison of these methods was recently published by Dominik Marx and Jürg Hutter.^[50]

Applied to the problem of interest here, all these methods offer some advantages, at least in principle. They give direct access to thermodynamic quantities and suitably averaged structural information at experimentally relevant temperatures.^[51] As long as actual molecular dynamics are performed, they also offer direct insight into dynamical processes, in the case of classical MD on empirical potentials even for very large biochemical systems.^[52, 53] But there are also some disadvantages. Path integrals only give (quantum) statistical mean values, no true quantum dynamics of the nuclei (“centroid MD” does provide semiclassical dynamic of the nuclei). For large systems, one cannot even approximate quantum dynamics with purely classical dynamics (in the sense of a quasiclassical treatment, as in typical reaction dynamics applications). For these reasons, the explicit insight into dynamics is actually limited to more or less representative single trajectories.

For sufficiently good statistics and systems of nontrivial size, the computational expense is very large, even for classical dynamics on empirical potentials. Substituting empirical potentials with direct DFT or ab initio treatments puts severe limitations on the treatable statistics and/or system size, even today. As a representative example, we mention the CPMD calculation performed by Chelikowsky and Dean on the thermodynamic quantities for Si_n ,^[51] which had to stop at $n = 5$ in spite of the use of supercomputers. A treatment at the DFT level may not be good enough for certain systems, and with the more reliable treatment of electron correlation in ab initio methods any approach to larger systems becomes completely impossible.

2.2. Alternative and Complementary Approach: Global Geometry Optimization

Considering the difficulties of methods aiming at complete dynamics or statistics, alternatives appear desirable. A simple hypothesis states that the cluster structure most likely to be found in experiments corresponds to the minimum of lowest energy on the potential energy surface (the justification of this hypothesis is discussed in Section 2.2.3). Therefore, alternative methods are those that are able to locate the global minimum among a large set of local minima, that is, global optimization methods.

2.2.1. Importance of Global Optimization in Chemistry

Actually, many-body problems are prevalent everywhere in chemistry. All systems under study consist of many electrons, many atoms, and perhaps even many molecules. Hence, one

could expect to see global optimization being used very often. There are several reasons why this is not the case:

1. In the electronic configuration (with the nuclei kept fixed) present-day knowledge indicates that multiple minima are not problematic and rare, at least in the vicinity of equilibrium structures. Accordingly, this aspect of the electronic problem is not discussed and with few exceptions not even mentioned in most textbooks.^[54]
2. On the other side of the Born–Oppenheimer separation we face the problem of the nuclei. Here, extensive prior knowledge about chemical structures and reactions leads to accurate guesses for structures of traditional molecules, which then only need to be optimized locally. For this reason, efficient local-optimization routines are present in every (quantum) chemical program package, while global ones are usually lacking. This approach does not work anymore for supramolecular structures, clusters, and similar systems; but this was not a pressing concern since structures of this size were not amenable to exact calculations anyway, until recently.

Nevertheless, various global optimization methods are currently being used in many areas of chemistry, a few examples are: the actual control of chemical reactions with lasers (following the basic idea “teaching lasers to control molecules” of Judson and Rabitz;^[55] this approach was realized experimentally in 1998^[56]), “molecular docking” in pharmaceutical lead discovery,^[57, 58] analysis and prediction of protein folding,^[58, 59] crystal-structure analysis^[58, 60] and prediction.^[61, 62] A review by Judson^[63] gives several other applications, with a focus on evolutionary algorithms.

2.2.2. Global Optimization Methods

In contrast to a common prejudice, local and global optimization are two very different tasks, requiring very different solution strategies. In local optimization, we have a general, problem-independent model (approximation by a quadratic form), which substantially enhances the efficiency of many methods; currently, such a model is unknown in global optimization. In local optimization, further information on the function to be optimized, in the form of first and second derivatives, is very useful; the local character of this information makes it largely useless in global optimization. Local optimization depends on the starting point by definition; whereas global optimization is independent of it, in fact, this is an important criterion for its success. Local optimization has a natural, universal end which is easy to test; whereas there is no safe termination criterion in practically relevant global optimization.

Another important difference in practice is the scaling of computational effort with problem size. Modern local algorithms scale only quadratically.^[64, 65] General global methods (without prior information on the structure of the function to be optimized) that actually give a guarantee for finding the global optimum scale exponentially, at least in the present application: It was demonstrated in an abstract fashion (independent of any potential) that global cluster geometry

optimization is an NP-hard problem (Table 1).^[66–69] This result means in practice that the search space and with it also the number of local minima increases exponentially, as was empirically found for small LJ clusters a long time ago.^[67, 70] Apparently, this is not only a basic problem for global optimization but also one of the reasons for intrinsic difficulties of any MD simulation of larger systems.

Such exact, deterministic methods (with a guarantee for finding the global optimum) exist in many variants today and are treated in standard monographs.^[71, 72] We will not further address these methods here, since their applications are limited to small systems, because of the NP character of the problem and to the implicit need for searching the complete configuration space. In the standard benchmark system of Lennard-Jones clusters (cf. Section 3.1), a DC transformation (Table 1) could be applied in exact form only up to $n = 7$;^[73] a homotopy method could handle clusters up to $n = 31$ (which are still trivially small for the methods discussed below) but surprisingly failed for three smaller cases.^[74]

This is the basis for practical relevance of “nonexact, nondeterministic” methods. There, the guarantee for finding the global optimum is deliberately dropped, in favor of a higher efficiency, which makes it possible to treat much larger systems. In the following, “global optimization” always means one of these nonexact methods. Because of the limited space available, we will not give an overview over all these methods, but only a brief, exemplary discussion of a few prominent algorithms.

The factual standard procedure in theoretical chemistry consists of successive local optimizations with excessive use of external prior information. The choice of initial starting points for local optimizations can be automated in several ways:^[72] simple random search, systematic grid search, “branch and bound” approaches, or selection of points on classical trajectories. Alternatively or additionally, arbitrary amounts of prior information can enter the choice of initial points. In any case, for a growing number of initial points the method converges towards a quasideterministic algorithm with an effective guarantee for finding the global optimum, simply because at some stage all the minima will have been found. But this is a rather theoretical limit; already for medium-sized clusters, this method will generally fail in practice, because of the exponential size scaling of the search space. The chances of missing whole regions of configuration space are already dangerously high for applications to small clusters. As an example, we mention the discovery of a clearly physically wrong global minima on a very elaborate silicon potential by using evolutionary algorithms,^[75] which escaped the attention of the authors of this potential^[76] when using successive local optimizations, in spite of their otherwise very careful work.

After its introduction,^[77] “simulated annealing” (SA) quickly became fashionable as a quasigeneral global optimization tool; but nowadays it faces some criticism: Computational expense is rather high compared to the final result (ideally just the global optimum), information permanently generated during the algorithm is not really used later, and finding the optimal cooling schedule turns out to be problematic in practice. There is a deplorable lack of fair comparisons,

but from my experience, SA in its original forms is not competitive with evolutionary algorithms for global cluster geometry optimization.

Recently, a distant relative of SA has gained interest, the so-called “basin hopping”. This method was introduced by Li and Scheraga^[78] for protein folding and adapted by Wales and Doye^[79] to the problem of cluster structure; meanwhile, there are also applications in other areas.^[80] Basically, this algorithm does a series of MC steps, which are followed by local minimizations; this corresponds to an MC treatment on a modified potential energy surface, which is transformed by the local minimizations to a series of plateaus and steps with fewer and lower barriers in-between; this is diagnosed as the basis of the success for this method. Because of the large number of local minimizations, computational expense is rather high for this method. Nevertheless, it seems to be the most efficient method today for small LJ clusters^[79] up to about $n=100$. Its size scaling is approximately n^5 , though, which limits its applicability to larger systems.

In the methods mentioned so far, one typically finds iterative improvement of single points in configuration space (that is, of cluster structures) without any exchange of information. In contrast, evolutionary algorithms (EA) are based on different ideas: A whole “population” of different cluster structures is treated quasi-simultaneously (which makes an efficient coarse-grained parallelization very easy). Various operators, some of them modeled after natural evolution, change these structures (“mutation”) or exchange (partial) structural information between them (“crossover”). This generates from the initial (random) population a new “generation” of cluster structures. Iterating this scheme over many generations results in a global optimization algorithm, and again a general one. Its result is not only the global optimum (upon convergence), but also a list of several good local optima. EAs are not new; the basic idea surfaced in the 1950s and was then rediscovered independently at least ten times (Fogel^[81] gives a historical account), sometimes under different names, for example genetic algorithms (GA), but these technical distinctions are largely obsolete today. A good introduction for beginners is given by Michalewicz and Fogel,^[82] applications in chemistry have been collected by Judson^[63] and applications to clusters by Johnston and Roberts,^[83] see also the documentation of the most recent developments in ref. [84]. My pioneering work in applications of EAs to global cluster geometry optimization is given in ref. [85]. With important additions of other groups,^[86, 87] these first steps could be developed into an efficient method,^[88] as reliable and about as efficient as “basin hopping” for small LJ clusters, but because of its cubic size scaling applicable also to larger clusters (up to $n=150$ already in ref. [88], and up to $n=250$ in ref. [89]).

Systematic and fair comparisons of such methods are very rare in the literature, and often limited to small systems.^[90] At least for the benchmark system of LJ clusters, which was treated with a wide variety of global optimization algorithms,^[67] “basin hopping”,^[79] and EAs^[88, 89] seem to be the only methods able to treat also the notoriously difficult cases $n=75-77$ and $n=102-104$ without prior information.

2.2.3. Status of the Global Optimization in Comparison to Traditional Approaches

For determinations of minimum energy structures, the expense of these alternative methods is smaller than for full MD calculations, because there is no need to generate statistically relevant trajectories. As results one gets directly the global minimum energy structure and energetically low-lying local minima. In comparison to typical MD and MC calculations, this allows a faster and more direct deduction of dependencies between terms in the potential energy function and structural preferences; this obviously simplifies the construction and improvement of empirical potentials for clusters. As for MD and MC, direct combinations of SA and EA methods with DFT calculations in simple or reduced form is possible for small systems and was already started several years ago.^[91–94] Direct combinations of all of these methods with better ab initio calculations are not practicable in general, since the computational effort is extremely large. As an example, we could show that MD–SA on the generalized valence bond (GVB) level with a “large core” pseudopotential works as expected for Ni_5 —in the sense that two trajectories starting from two totally different structures reached the same final minimum.^[95] This level of treating the electronic structure, however, is not sufficient in this case: The planar W-structure we found turns out to be incorrect at higher levels. The correct structure presumably is that of a deformed trigonal bipyramid,^[96a] experimental results^[96b] seem to confirm this.

We tried an indirect approach and found this to be more successful: In an SCF-like cycle, global geometry optimizations on an empirical potential alternate with successively better fits of this empirical potential to ab initio single-point calculations (at just these minimum structures), by global optimization of the parameters in the empirical potential. Shortly after its introduction,^[75] this strategy was applied successfully to atomic silicon clusters^[97] and mercury clusters^[98] as well as to molecular water clusters.^[99] In practice, this method reliably yields the global minimum energy structures on the DFT or ab initio potential, and also an improved empirical potential.

As opposed to MD and MC calculations, global minimizations are purely static, in the sense of producing only the (classical) global minima of energy (enthalpy). With appropriate vibrational analyses of the sets of local minima, however, which are additionally obtained, one can extend the results up to full thermodynamic data,^[100, 101] and with sufficiently large data sets of minima and transition-state geometries, through a master equation, approach even approximate relaxation dynamics.^[102, 103] In spite of these possible refinements, MD and MC methods do not become superfluous; in my opinion these methods are complementary. For certain research aims, for example, the structural transitions envisaged here, or the relationship between potential and cluster structure, searching for the global minimum is an answer to the zeroth-order question. Effects of zero-point energy, finite temperatures, and cluster dynamics are secondary considerations. For many of the systems mentioned in Section 3, experiments do indeed find the global

minimum energy structures. There are also counter examples, though, as demonstrated with the water hexamer (see Section 3.5). The identification of such cases as counter examples can still be done with global optimization, but further investigations have to include the traditional methods.

3. Exemplary Systems

3.1. LJ Clusters as Models for Noble-Gas Clusters

Clusters of noble-gas atoms are typically modeled using the LJ pair interaction. Stone's book^[104] provides an introduction to this potential, including its partly absent physical basis, and shows improved alternatives.^[105, 106] Hence, the LJ potential is mainly of historical importance, because of its analytical simplicity. But for this same reason it is still used in many places even today, for example, also as a compulsory benchmark system for global cluster geometry optimization methods. Extensive lists of structures and energies of global and local minima are available on the internet.^[107, 108] There is such a vast amount of literature on this topic that perhaps every global optimization method in existence has at sometime been tested on this LJ benchmark system.^[67, 70, 79, 87–89, 109] (Applications of this type to the more advanced noble-gas potentials are extremely rare.)

Therefore considering the huge amount of data known, the discovery of a new (fourth) structural type of LJ clusters in 1999, as a new global minimum for LJ₉₈, was quite a surprise.^[110] This simple fact illustrates that the LJ system is all but simple, in spite of its simple potential functional form.

Figure 2 shows the four known basic structural types of LJ clusters, which feature different fundamental arrangements: Icosahedral structures are the logical continuation of the icosahedral scheme already introduced in Section 1.2, starting from the pentagonal bipyramid and continuing beyond the icosahedron itself by addition of further atom layers (which

can happen in different ways.^[108, 109]) The fcc (face-centered cubic) structures are sections from the fcc crystal. Decahedral structures can be visualized as an icosahedral core surrounded by fcc stacks. The new tetrahedral structures actually have a tetrahedron of atoms as the innermost core.

As mentioned in Section 1.2, icosahedral structures can be expected to be optimal, since they are (almost) a packing of tetrahedra and thus maximize the number of nearest neighbors. In three dimensions, however, such a packing cannot fill space exactly. Therefore deviations from the ideal pair distance arise, which can be interpreted as strain.^[111, 112] This strain increases with cluster size. The other structural types are less strained, but have reduced numbers of nearest neighbors. Hence it comes as no surprise that the global minimum energy structures of smaller LJ clusters follow the icosahedral scheme almost without exception. This trend was analyzed in detail by Doye, Miller, and Wales, up to a size of $n = 80$ ^[113] (Figure 3; at that time, the fourth tetrahedral

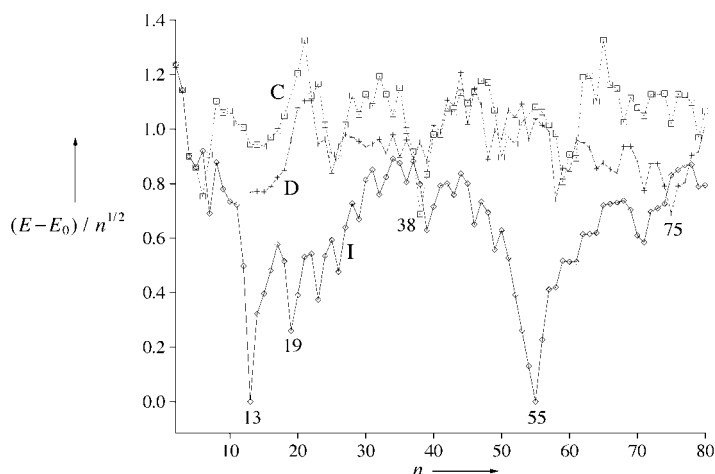


Figure 3. Competition between three of the four structural types of LJ clusters, in the size region up to $n = 80$: I = icosahedron, D = decahedron, C = face-centered cubic. The energy axis is scaled such that icosahedral clusters with closed shells ($n = 13$ and $n = 55$) have zero energy ($E_{13} = E_0$; $E_{55} = E_0$); reproduced with permission from ref. [113].

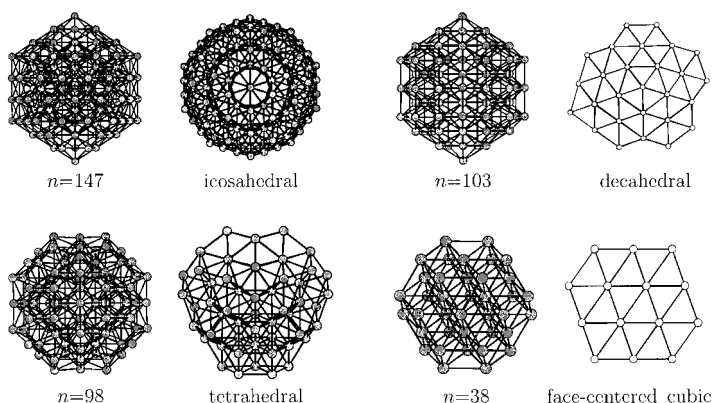


Figure 2. Pairs of views of each of the four basic structural types of LJ clusters; for each type: left: a projection that emphasizes the approximately spherical outer form; right: the same cluster in a different projection that emphasizes typical features of the inner structure (here, various numbers of atoms are projected on top of each other). At the number of atoms n indicated (but also at other cluster sizes), these structures have globally minimal energy; see text.

structural type was still unknown): These and other investigations showed that fcc and decahedral structures come close in energy to the icosahedral ones only around cluster sizes $n = 38$, $n = 75 - 77$ and $n = 102 - 104$ and actually provide the global minima only at these particular cluster sizes themselves. These sizes are between the icosahedral shell closures of $n = 13, 55, 149, \dots$, but not exactly in the middle; in fact, there is no simple explanation yet for their occurrence at exactly these sizes. But even at these LJ cluster sizes, the search space is dominated by icosahedral structures, which makes these clusters particularly hard test cases for global optimization methods.

Icosahedral structures of noble-gas clusters were actually observed experimentally in argon molecular beams.^[114] There are contradictory speculations about their role in other situations, in particular, in seed formation for crystal

growth.^[28] A tempting but provocative hypothesis says that icosahedral growth is actually a dead end for crystal growth.

This picture of almost complete dominance of icosahedral structures appears to continue at least up to $n=250$,^[89] perhaps even up to $n=309$ ^[108]—but the LJ periodic crystal cannot contain fivefold rotation axes! In the experiment, it is actually fcc. This shows again the deficiencies of the LJ potential, because theoretical predictions of solid-state structure based on this potential arrive at the hcp form (hexagonal close-packed).^[115] Not only the three-body terms missing in the LJ potential but also zero-point energy differences apparently lead to fcc rather than hcp^[116] (even these calculations still have some model characteristics, since they are not completely ab initio and use some approximations). Therefore, there has to be a transition from icosahedral structures to fcc ones somewhere, perhaps with decahedral structures as intermediate stage. But that is already where our knowledge ends and speculations begin: from experiments, the transition is put somewhere in the range $n=750–800$,^[114] while theoretical approaches point to the range $n=1500–10000$ ^[117] ($n=10179$ corresponds to an icosahedral cluster with 14 filled shells^[19, 20]). Recent MD studies^[118] try to model the transition explicitly dynamically, and claim better agreement with experiment by a dynamical coexistence of several (imperfect) structures.

Doye and Calvo^[119] have pointed out that the exact positions of these structural transitions also depend on entropy, which can have different contributions to the Gibbs free energy of the different structural types. Therefore, part of the discrepancies between different experiments may be a result of different temperatures.

Alternative explanation attempts by faulted cluster models^[26] at first appeared to provide a successful synthesis of fivefold centers and the fcc solid state, which also could have explained the advantage of fcc over hcp by preferential crystal growth into the fcc direction. But this could not be verified, on the contrary: the most recent modeling of the experimental data^[120] are interpreted as proof for fcc, hcp, and rcp regions (random close packed) side by side in larger clusters in the experiments, in about equal amounts. This interpretation leads to the conclusion that these experimental systems (probably because of their preparation) cannot be used to study the transition from icosahedral structures to fcc.

In summary, LJ clusters are a seemingly trivial system which then turns out to be very complicated and exciting. The decisive size region of structural transitions is at rather large cluster sizes and hence difficult to reach with any of today's methods. Even the apparently simplest questions (which structure dominates for which reason in the solid state, and how do small clusters develop towards this structure?) are still wide open, in spite of frequent applications of many advanced techniques. This in some way simplest system is only of academic interest for most chemists. Therefore, these big gaps in our knowledge of this system show the limited abilities of our modern theoretical and experimental methods in this area, and this tells us to drastically lower our expectations for more complicated cases in “actual chemical applications”.

3.2. Further Simple Systems

3.2.1. Non-Noble-Gas van der Waals Systems

The transition to fcc in other systems with van der Waals interactions (N_2 , CO_2 , etc.^[121–123]) occurs at much smaller cluster sizes (e.g. about $n=30$). As an explanation, it is proposed that it is the anisotropy of molecular systems that leads to a generally larger strain. According to the analyses of Berry, Doye, and Wales^[111, 112] strain increases with cluster size in icosahedral geometries, and larger anisotropies favor more densely packed geometries;^[124] therefore, the transition from icosahedral to fcc geometries can be shifted to much smaller clusters. This tendency makes these systems much more amenable to theoretical approaches; so far, however, they have been much less investigated than the isotropic LJ system.

3.2.2. Morse Cluster

Variation of one further parameter, the width of the potential well in the pair interaction, leads from the LJ potential to the Morse potential (Figure 4). Global optimization studies of Morse clusters^[125] arrive at the same basic structural types as mentioned above for LJ clusters, but there

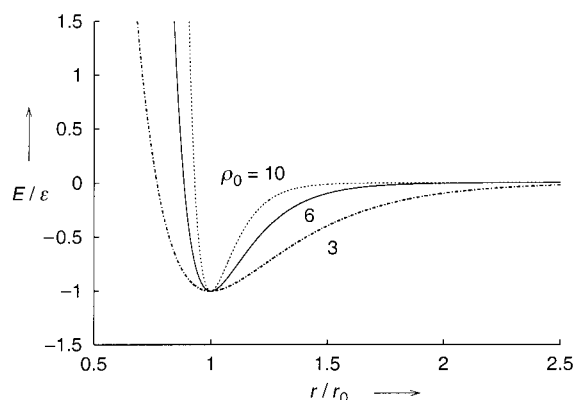


Figure 4. Variation of well width ρ_0 of the Morse potential (energy E in units of well depth ϵ as function of distance r in units of the equilibrium distance r_0); for $\rho_0 \approx 6$ the Morse and LJ potentials are the most similar.

is a further complication: the structural type of the global minimum of smaller clusters does not depend solely on cluster size anymore, but can be changed by variation of the well width to any of the other structural types (Figure 5). This phenomenon can again be understood qualitatively with the above strain argument: variation of the well width directly changes the energy costs associated with deviations from the optimal pair distance, and thus also changes the contribution of strain energy to the total energy. Since the different structural types have different strain, the well width in turn influences the energy competition between these structural types.

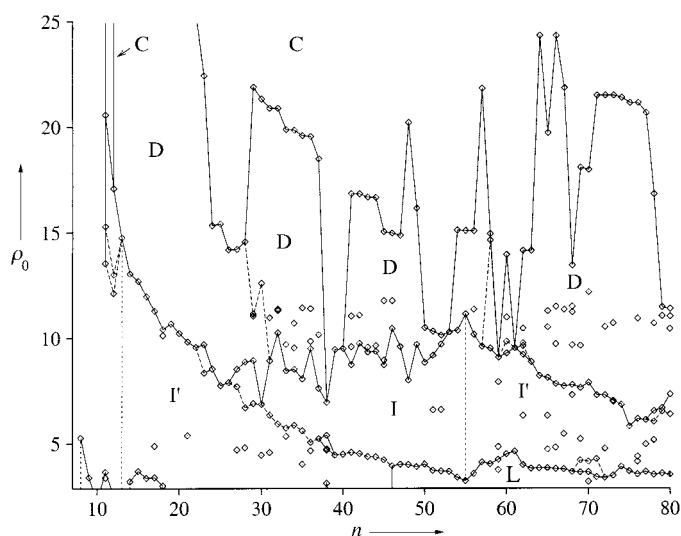


Figure 5. “Phase diagram” of Morse clusters: Change of structural type of the global minimum with cluster size n and with well width ρ_0 of the Morse potential (compare with Figure 4); abbreviations as in Figure 3; reproduced with permission from ref. [125].

3.3. Silicon Clusters

All the systems mentioned above are model systems with only simple pair interactions between the particles. The diversity of chemistry, however, is largely induced by more complicated interactions, which can be treated approximately by many-body terms, which lead to preferences for certain bond and dihedral angles. Accordingly, clusters of more realistic systems can be expected to exhibit other characteristic structures and other structural transitions. This behavior is shown for silicon clusters as one prominent example.

There has been experimental and theoretical interest in silicon clusters for quite some time; among others, Jarrold^[126] and Smalley and co-workers^[127] have offered reviews of this topic. Historically, small silicon clusters were first assumed to be simply pieces of the silicon crystal lattice. This notion was soon disproved by the observation of the surprisingly low reactivity of these particles,^[17] which did not fit the common expectation (small particles have a larger surface area for their volume, and hence are more reactive). In this vein, attempts to construct structures for silicon clusters with similar surface reconstructions as bulk silicon^[16] also turned out to be a misconception, since this cannot explain their reduced reactivity compared to the bulk.

After some dispute in the past, there is now good agreement between theory (QCISD/6-31G\ast level) and experiment (IR and Raman spectra) for the smallest clusters ($n \leq 7$).^[128–131] Here we have agreement between experimental structures and theoretical global minimum energy structures. For larger clusters up to $n = 10$, there also appears to be agreement between various theoretical calculations with regard to the global minima. At $n = 10$ itself, the tetracapped trigonal prism (TTP) is now generally favored (Figure 6).^[97, 132] This structure is unknown in the icosahedral growth pattern of LJ clusters, and also the smaller silicon

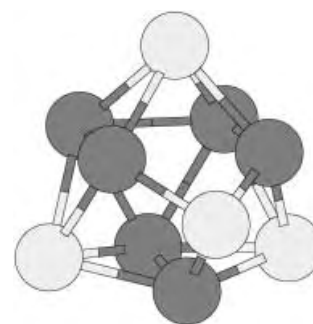


Figure 6. Global minimum of Si_{10} : tetracapped trigonal prism; the atoms at the corners of the trigonal prism are shown in dark, the capping atoms in light color.

clusters deviate from this pattern, with few exceptions, for example, the pentagonal bipyramid at $n = 7$.

For larger clusters, discrepancies set in. There is a large number of DFT studies with local minimization of guessed starting geometries,^[16, 133] a dangerous way to proceed for clusters of this size (see Section 2.2). Probably more reliable are CPMD-SA studies,^[134] but these were performed only for $n < 10$ and $n = 33, 45$, without the interesting size region in-between. Other works used still less reliable treatments of the electronic problem (semiempirical methods, such as AM1^[135] or “tight binding” (TB)^[136–140]), but some of them did employ global geometry optimization.^[139] The overall impression of these and many similar studies is that of differences between each other and to the experiment.^[141]

The most prominent experiments in this area with nearly direct structural information in the size region $n > 12$ are mobility measurements of silicon clusters in helium gas.^[142, 143] Comparison of the resulting data with trajectory calculations^[144] or projection approximations of hard spheres allows the determination of the outer form of these clusters (but not of their inner structure). According to these results, clusters in the size region $10 \leq n \leq 20$ are not spherical but markedly prolate (elongated), in the region $24 \leq n \leq 28$ there is a structural transition with several coexisting forms, and still larger clusters are mostly near-spherical oblate.

These structural transitions are confirmed by a collection of experimental binding energies, indirectly deduced from several experiments in the size region $5 \leq n \leq 75$ ^[145, 146] and directly measured by calorimetry^[147, 148] in the region $65 \leq n \leq 890$. These data can be compiled into one single, consistent picture (Figure 7), which again shows this structural transition in the same size region.

Recently, by using a simple EA strategy directly on the DFT level in the size region $10 \leq n \leq 20$, Jarrold and co-workers^[141] have found prolate cluster structures that agree with the experimental mobility data and feature TTP as basic building block. Figure 8 shows a typical member of this set of structures. These results were then confirmed in various ways: Jarrold’s group investigated the energetics of various dissociation pathways^[149, 150] and found consistency only for these new structures. Frauenheim and co-workers^[94] applied a DFT-based TB scheme in a simplified EA structural optimization and arrived at qualitatively similar structures, with some quantitative improvements, but still in agreement with the

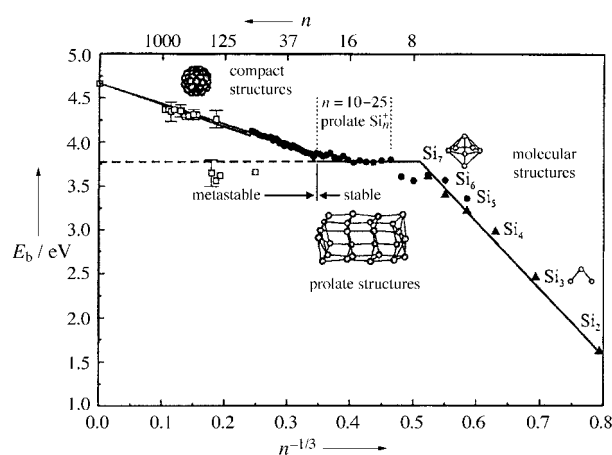


Figure 7. Binding energy per atom (E_b) of Si_n as function of cluster size (inverse cluster radius $= n^{-1/3}$); in this common axis scaling,^[22] changes in trends are visible as changes in slope of linear fits; data of several experiments^[145–148] are shown; reproduced with permission from ref. [148].



Figure 8. One proposed structure^[144] for Si_{20} , build from two Si_{10} units in TTP form; colors of the atoms as in Figure 6.

mobility data. Now there are also spectroscopic measurements further confirming these structures.^[151] This accumulated evidence suggests that we now “understand” this size region $10 \leq n \leq 20$.

Nevertheless, a few points still require clarification: the level of theory mostly used (DFT, or DFT-TB) is perhaps not sufficient; for some small clusters, DFT fails, and the energy differences between different isomers decrease with cluster size, so that small errors have a large effect. Furthermore, a general understanding beyond a black-box agreement between experimental and theoretical results seems to be lacking. For example, there is no explanation why TTP should be a good building block for larger clusters. TTP is one of the so-called “Bernal holes” in random close packings of hard spheres^[18] and is perhaps also important in the seemingly completely different system Hg_n (Section 3.4); but why TTP is here (and perhaps in Hg_n) a particularly stable and preferential building block remains unclear.

If one concedes that the size region $10 \leq n \leq 20$ is nevertheless explained, there is still the region $24 \leq n \leq 28$ with the actual structural transition. The first investigations of this area have been made,^[152] but only on the DFT-TB level, for a few selected cluster sizes ($n = 25, 29, 35$), and without direct comparison to the experimental mobility data. Future work still needs to explain why further metastable isomers are reproducibly observed far beyond the structural transition^[147, 148] and which new structural principles come into effect at the structural transition: If TTP is still a good building block, how is the observed transition in the outer form of the clusters possible? Or, if TTP does not occur in

larger clusters, why does it stop to be a good building block at these cluster sizes?

As a final remark it must be emphasized that there are big differences between silicon and carbon clusters^[86, 137, 153, 154] (this will come as no surprise to inorganic chemists). Small carbon clusters are usually linear or circular; there are no such forms in Si_n . The existence and stability of fullerene-type structures for pure Si_n is still disputed, in spite of many studies on this topic;^[155] current evidence is not favorable.

3.4. Mercury Clusters

Smallest clusters of metallic elements show no metallic properties; these set in only from a certain cluster size, depending on the element and on the property under study.^[12, 22, 156]

An important example for this phenomenon is provided by mercury clusters.^[157] Several experiments^[158–166] indicate that there is a nonmetal–metal transition in mercury clusters, but the size range is disputed: theoretical estimates and experimental evidence vary between $20 \leq n \leq 70$,^[159] $n \geq 100$,^[160] and $n = 400$.^[161]

Simple theoretical reasoning, highly accurate CCSD(T) calculations,^[167] and experiments arrive at a very low binding energy and large atomic separation for Hg_2 , underpinning its van der Waals character. Various experimental and theoretical details^[160, 168] lead to the expectation that this character continues up to about $n = 13$. Approximately from this cluster size onwards, covalent character is expected, until the actual transition to the metal at still larger sizes. Hence, we have not one but two transitions in bonding character, and there should be some evidence for this also in the corresponding cluster structures.

There is, however, an acute lack of structural information from experiments. Some expensive theoretical calculations^[169–171] relied on structural hypotheses derived from the above expectations; comparisons with experiment still leave some room for improvement. Less expensive studies with model Hamiltonians^[172] or at the DFT level^[173] can avoid structural hypotheses but are not sufficiently accurate; model Hamiltonians are based on assumptions of a certain bonding character, and DFT is known to be problematic for systems with long-range van der Waals type interactions.

Already at the smallest cluster sizes global minimizations on highly accurate ab initio levels are much too expensive for this system. Therefore, an ab initio/empirical hybrid model^[171] was used in conjunction with the EA methods explained in Section 2.2 to arrive at global minimum energy structures^[98] for Hg_n , $n = 7–14$. These structures deviate surprisingly strongly from the icosahedral growth scheme which should clearly be expected for a pure van der Waals system in this size region. Icosahedral structures can be found at some cluster sizes as high-energy local minima, but all global minima have completely different structures (Figure 9). At $n = 7$ and $n = 10$, structural and energetically particularly prominent clusters are found: in this hybrid model, Hg_7 has the astonishing structure of two tetrahedra joined at a common tip. Hg_{10} surprises by having qualitatively the same

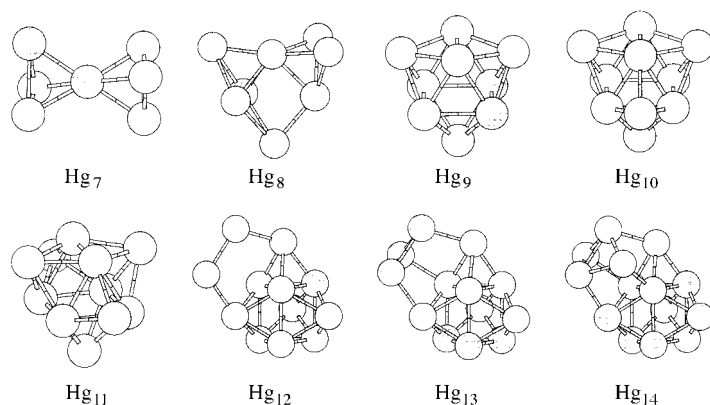


Figure 9. Proposed global minimum energy structures^[98] for Hg_n , $n = 7 - 14$, in a quantum mechanical/empirical hybrid model; the icosahedral build up typical for van der Waals systems is not discernible, structures of this type are at best high-energy local minima (not shown here).

TTP structure as Si_{10} . There is no direct connection to experimental data yet, for example, in the form of calculated ionization potentials. Nevertheless, the special roles of $n = 7$ and $n = 10$ seem to be quite in agreement with experiment.^[98] A closer examination of the published experimental data^[158, 174] shifts the transition from van der Waals to covalent character (which was put at $n = 13$ largely because of the hypothetical icosahedral structure) to $n = 11$ (Figure 10). This

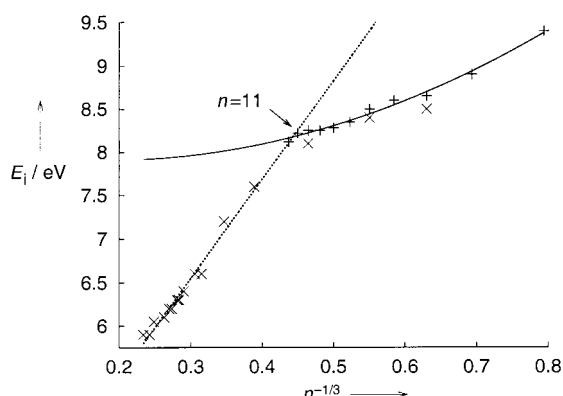


Figure 10. Trends in experimental ionization potentials E_i of Hg_n ; data of several experiments (+: Cabaud et al.,^[158] ×: Rademann^[174]) are plotted as a function of cluster size (inverse cluster radius = $n^{-1/3}$), as well as a linear fit for the limit of large clusters and a quadratic fit in the region of small clusters. The transition between these two occurs close to $n = 11$.

again is in better agreement with the new structures, since after one further capping of the TTP structure at $n = 11$, a new geometric shell has to be established upon transition to $n = 12$. This hybrid model was tested only for very small mercury clusters. Currently, single point calculations for larger clusters are being carried out to check the model for larger clusters. In any case, the above findings indicate that the simple and obvious picture of a transition from van der Waals to covalent character at the first icosahedral shell closure ($n = 13$) is perhaps too simple. Even if the structures shown here are not fully correct, there is either no direct connection between bonding type and cluster structure, or the pure van der Waals character is already lost in very small clusters. Furthermore, a

lot of theoretical development work still needs to be done before one can even start to think about investigation of the transition to the metal at still larger cluster sizes.

3.5. Pure Water Clusters

Pure water clusters were recently reviewed by Ludwig.^[175] From the different point of view of the present article, to provide a transition to the following Section 3.6, and to supply a few additions, we want to consider these systems briefly.

The smallest clusters $(\text{H}_2\text{O})_n$, $n = 2, 3$, have been treated in a highly exact fashion by electronic structure theory^[176–178] as well as by nuclear dynamics calculations,^[179] in excellent agreement with experimental results (ref. [180] older literature cited therein). From this, we know that the level of quantum mechanical treatment of the electronic structure should at least be MP2, pure HF calculations are not sufficient: the dimer interaction energy at HF level amounts to only $-14.85 \text{ kJ mol}^{-1}$; MP2 contributes a substantial addition of $-6.276 \text{ kJ mol}^{-1}$, whereas correlation contributions at still higher levels give only another $-0.21 \text{ kJ mol}^{-1}$.

Another lesson from these publications (as well as earlier ones in this area) is that it is very difficult (if not impossible^[181]) to find an empirical potential that reproduces the properties of water in as diverse surroundings as clusters, fluids, and the solid state. Fitting a suitable functional form to the ab initio results mentioned above yields a potential that reproduces the tunneling splittings in the spectroscopic experiments mentioned above very well,^[182] but this accuracy appears to be rather limited in configuration space: Simulations of liquid water with this potential result in pair distribution functions that deviate more from experimental results than those stemming from much simpler potentials, such as TIP4P.^[183] Therefore, it seems more promising to build a potential on a much broader basis of ab initio data.^[184]

For potentials as different as TIP4P^[185, 186] and ab initio MP2,^[99, 187] some cluster structures are nevertheless qualitatively the same: Small clusters up to $n = 5$ are rings, and larger clusters with $n \geq 7$ have three-dimensional structures. The necessary structural transition in-between seems to be very close to $n = 6$, and therefore we see a large structural diversity for the hexamer, with very small energy differences between qualitatively different isomers: at a temperature of absolute zero and without zero-point energy, the prism clearly has the lowest energy at any suitable ab initio level,^[99, 187] followed by several variants of the cage. Quasiplanar structures as the book and the six-ring are still higher in energy (Figure 11). In the limited spectral region of the experiments by Saykally et al.,^[188] only the cage form is found. Even if signatures of other forms may still hide in unexplored regions of the spectrum, the estimated temperature of the experiment (about 5 K) is consistent with the presence of just one isomer, in spite of the small energy differences. This discrepancy between theory and experiment seems to be removed by addition of zero-point energy corrections,^[189] even if one fully trusts the empirical potential necessary to evaluate these corrections by quantum Monte Carlo (QMC) calculations

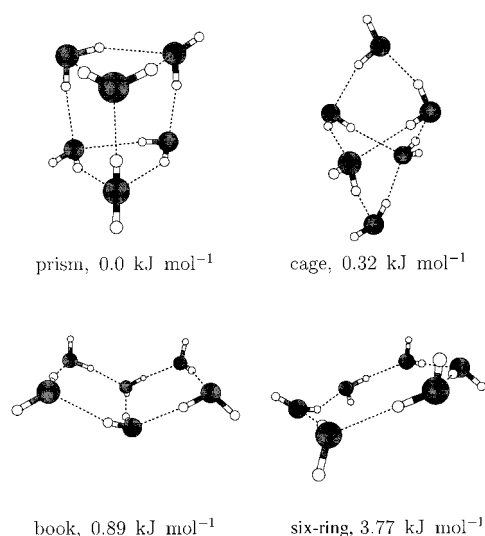


Figure 11. Global and local minimum energy structures of (H₂O)₆ at LMP2 level (Table 1) with an aug-cc-pVTZ basis set;^[99] energies relative to the prism (without corrections for zero-point energy and finite temperatures).

(instead of a more exact *ab initio* surface), some doubt still remains, simply because the errors in the large zero-point energy corrections may be larger than the small energy differences of the isomers before and the still smaller energy differences after applying these corrections. Kim and Kim^[187] have also claimed to get rid of this discrepancy with corrections for both zero-point energy and finite temperatures. But there are methodical problems also in this case, since the frequencies necessary for these corrections were calculated only in harmonic approximation, which is problematic for this system. Nauta and Miller^[190] found only the planar six-ring and no trace of prism or cage for the water hexamer inside helium droplets. Therefore, at least for $n=6$, the cluster structure actually found depends quite strongly on the preparation conditions, and this could be the case in Saykally's experiment, too. Hence, at this time we can only conclude that the exciting problem of the water hexamer is still an open one.

For somewhat larger clusters ($n=7-10$), there is still fairly good agreement between theory (MP2 and empirical potentials, empirical but anharmonic simulation of spectra) and experimental OH stretch vibrational spectra.^[191] Up to $n=11,12$, harmonic spectra at the MP2 level are available.^[192] For still larger clusters, these approaches become too expensive.

On the very simple empirical TIP4P level, global minimum energy structures are known with a fair amount of security up to $n=20$ ^[185, 186] and with reasonable probability up to $n=22$.^[186] Analysis of these global minima shows an almost complete lack of systematic structural buildup. At best, one can diagnose a preference for cubes and pentagonal prisms and structures assembled from these units, which is not quite in agreement with chemical intuition.

Surprisingly, one also finds that in all of these global minimum structures (with the sole exception of $n=19$) all the water molecules are on the surface of the cluster (Figure 12). A transition to structures with inner water molecules obviously has to occur with increasing cluster size, but the critical size for this transition has not yet been located reliably.

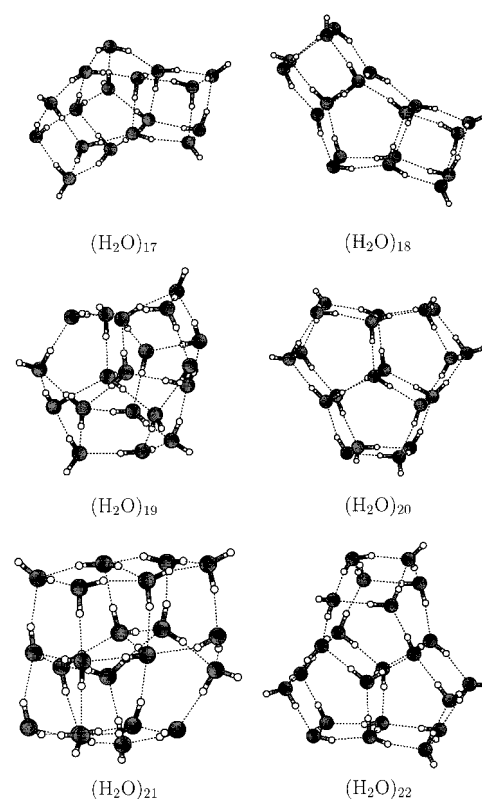


Figure 12. Global minimum energy structures^[185, 186] of (H₂O)_{*n*}, $n=17-22$, for the empirical TIP4P potential. For $n=21$, one does not find a centered dodecahedron (cf. Figure 13) but again a structure assembled from (distorted) cubes and pentagonal prisms, with all the water molecules at the surface of the cluster.

Of course, TIP4P is an extremely simplified model. Global geometry optimizations^[193] (massively parallel on a CrayT3E) on the sophisticated TTM2-F potential^[194] (based on TTM2-*R*,^[184] with flexible monomers, and a very good internal water potential with nonlinear dipole surface by Partridge and Schwenke^[195]) confirm many but not all of these globally minimal TIP4P structures. Interestingly, deviating global minima are distinguished by a central water molecule; this happens for the first time at $n=17$ (Figure 13). Again in contrast to the TIP4P results, we find for TTM2-F at $n=21$ a (deformed) dodecahedral cage structure around a central water molecule. Both findings agree better with chemical

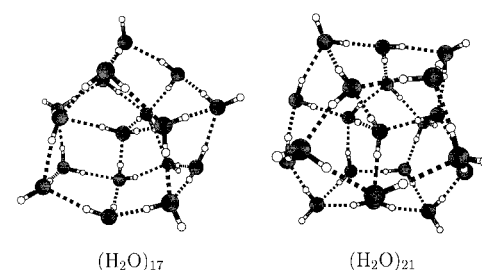


Figure 13. Global minimum energy structures^[193] of (H₂O)_{*n*}, $n=17$ and 21, for the *ab initio* adapted TTM2-F potential.^[194] Already for $n=17$, the best structure has one central water molecule, and for $n=21$ we find a centered (distorted) dodecahedron; both findings are in contrast to the TIP4P case (cf. Figure 12).

intuition and with corresponding results for ion microsolvation clusters (Section 3.6). In any case, the exact location of this structural transition obviously depends strongly on the potential used. DFT and MP2 calculations as well as *ab initio* and empirical MD simulations are currently underway in our group, to further illuminate this problem.

Because of the very small energy differences between minimum structures of larger water clusters, corresponding to an easily changed hydrogen bonding network, the very notion of structure starts to become questionable, and only dynamical mean values from MD or MC simulations retain some meaning. This method does not fully contravene the above approach of quasistatic global geometry optimization. As already discussed in Section 2.2.3, we perceive these two approaches as complementary. Global geometry optimization yields the desired information on the underlying potential energy surface faster and more directly, and this permits a better assessment of the effects of different model potential terms. Even in the presence of nonclassical “smeared” structure distributions over whole regions of configuration space it is still interesting and useful to know the potential minima behind this distribution, be it only for a proper diagnosis and analysis of this situation. In spite of this objection, in my opinion, the attempts to capture properties of ice and water with special cluster models^[196] for parts of the (dynamical) hydrogen bonding network are not misguided. Of particular interest here is the appearance of clathrate-like structures (Section 3.6), even if this is criticized by some authors.^[197, 198] At least as useful, are the direct contacts between theory (with MD studies of large clusters of 1000 molecules, using empirical potentials and model-based simulation of IR spectra) and experiments on ice aerosols which are currently beginning.^[199]

3.6. Ion Microsolvation Clusters

In this almost arbitrarily broad field, we only want to consider simple ions such as alkali cations and halogen anions with water as solvent, and we want to place the main focus on larger alkali cation water clusters.

Likewise, we will not attempt to give an overview of the extremely numerous experimental and theoretical studies on solvation in liquids. Nevertheless, some salient points of relevance here should be mentioned: recently, some experimental evidence on the reduced dynamics of hydrogen bonds in solvation shells of anions was published;^[200] of course, this gives considerable support to the concept of gas-phase microsolvation clusters as models for bulk solvation in the liquid phase. Many studies agree in assigning different tendencies of ions, such as Na^+ to bulk and Cl^- to surface solvation; for example, this is observed in *ab initio* and DFT calculations,^[201–203] in model potential studies of clusters,^[204, 205] and MD slab calculations.^[206] A consistent rationale of this observation apparently requires a combination of size and polarization effects.^[204–206] Even ions of much closer chemical similarity, as Na^+ and K^+ , have a different influence on the surrounding water (“structure-making” versus “structure-breaking”^[207]). Finally, these systems even have some bio-

logical relevance: there is an X-ray structure of a cell membrane ion channel,^[208] which differentiates between Na^+ and K^+ ions. The existence of this structure has intensified attempts to understand the mechanism of this selectivity. It does not come as a surprise that besides simple differences in ion size also the differences in solvation behavior could have some influence here.^[209–213]

Microsolvation clusters in the gas phase (several reviews^[214–217]) are often viewed as model systems for bulk solvation in the liquid phase. Obviously, there are some differences between these two situations, for example, in solvation clusters there are certainly surface artifacts, which are not present in the bulk solution. Also, exchange of solvent molecules may proceed in different ways in clusters and in the solution. Because of the experimental preparation conditions, the temperature region covered by clusters is presumably quite different (apparently below 150 K^[218]). Nevertheless, microsolvation clusters in the gas phase are at least an important intermediate step on our way towards a better understanding of solvation in solutions, simply because they guarantee more closely controlled and less “averaged” conditions, which is advantageous for both experiment and theory.

Today, microsolvation clusters are experimentally accessible by various methods.^[219–221] On the theoretical side, there are some *ab initio* studies of small clusters^[222, 223] for the systems of interest here, $\text{Na}^+(\text{H}_2\text{O})_n$, $n \leq 10$ and $\text{K}^+(\text{OH})_n$, $n \leq 6$, and also comparisons between *ab initio* calculations, empirical potentials with and without polarization, and experiment.^[224]

Of course, there are also very many studies of these microsolvation clusters with empirical potentials^[225–227] (see also further citations in these articles), but considering the vast number of empirical water potentials we refrain from discussing them. The work with TIP4P/OPLS modeling discussed below of course is relatively crude, but they are at least partially justified by surprisingly good qualitative agreement with the *ab initio* calculations mentioned above and with MC results on more elaborate potentials.^[228, 229] Among other things, experiments on solvation clusters of simple cations (the reviews cited above) also point to several magic numbers. One particularly outstanding item is the hypothesis of a dodecahedral clathrate cage of 20 water molecules around the central cation, independent of the type of this cation. This hypothesis is often ascribed to Castleman and Holland^[230] but its roots can be traced further back in the literature.^[231] Cage structures of this type but typically around hydrophobic guest molecules have been known for a long time as clathrate hydrates in the solid state. They occur in many natural and industrial situations^[232, 233] and are examined theoretically (ref. [234] and literature cited therein) as well as experimentally (refs. [235, 236] and references therein). Combustion of methane from deep-sea methane hydrates is currently being considered as a new source of energy.^[237, 238]

The casual naturalness of the clathrate hypothesis may have furthered its rather uncritical use as *ad hoc* structure hypothesis not only in microsolvation (from *ab initio* calculations^[239] all the way to experiments^[219, 220, 240, 241]), but also for the so-called “hydrophobic solvation” in the liquid phase, with

questionable success.^[197, 198, 242] Here, we are mainly interested in the experimental observation that $n = 20$ is a magic number for K^+ and Cs^+ ions but not for Na^+ ions, which is not immediately clear from the clathrate hypothesis.

A global geometry optimization study by Hodges and Wales^[243] on several empirical potentials verifies the clathrate hypothesis for H_3O^+ as the cation—however, with the cation not in the center but in the cage periphery. Ab initio calculations^[244] confirm this, recently also for NH_4^+ ions but again with slight modifications.^[245]

Systematic global optimization calculations^[221, 246] on the TIP4P/OPLS level confirm the ion-centered clathrate (with some modifications and refinements, see below) also for K^+ and Cs^+ ions, but they also show why Na^+ ions are different:^[221] there, an unexpected structural transition was found between $n = 17$ and $n = 18$, from cation-centered structures to geometries with the cation placed far off-center (Figure 14). A detailed analysis of different pair interaction contributions and energy partitionings leads to a qualitative understanding

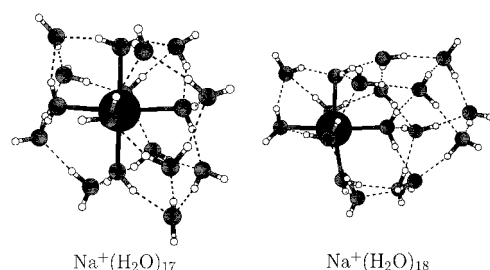


Figure 14. Global minimum energy structures^[221] of $Na^+(H_2O)_n$, $n = 17$ and 18 , for the empirical TIP4P/OPLS model. For $n \leq 17$, the Na^+ ion is at the center of the cluster, whereas it is strongly off-center for $n \geq 18$; this is in agreement with experimental observations.^[221]

of this transition.^[221] This off-center structural type also dominates for $n = 20$, and it is not consistent with a dodecahedron—even if the dodecahedron would have the cation in the periphery, because the Na^+ –water pair interaction is much too strong compared to water–water interactions to permit the concomitant partial loss of first-shell water molecules from the Na^+ ion (Figure 15). This structural transition appears to correlate with experimental results.^[221] Of course, the theoretical finding that $n = 20$ is structurally not special at all in $Na^+(H_2O)_n$ is also in agreement with the experimental findings^[220] and in contrast to the corresponding K^+ and Cs^+ ion clusters where $n = 20$ is a magic number.

These results also show that even for K^+ and Cs^+ ions the picture of an ideal dodecahedral clathrate cage for $n = 20$ is too much of a simplification^[246] (Figure 15). In both cases, the cage hull is heavily puckered and distorted, compared to the ideal dodecahedron. For the K^+ ion there are noncage structures very close in energy; and for Cs^+ ions, cages containing also four-rings and six-rings are very close in energy to the pure five-ring cage. Calculations at better levels of theory (also including temperature effects (entropy)) for this structural transition in the Na^+ ion case and for the various cage structures of alkali cations are currently being performed in our group.

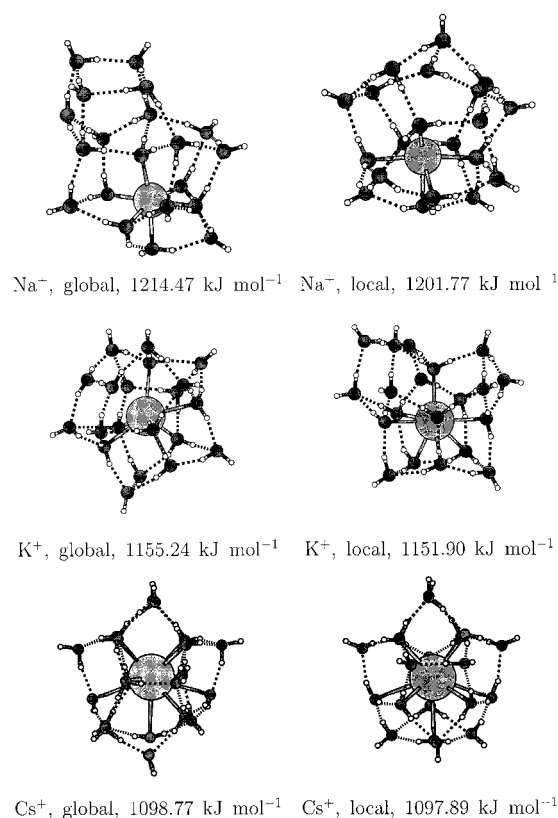


Figure 15. Global and local minimum energy structures^[246] of $M^+(H_2O)_{20}$, $M = Na, K, Cs$, for the empirical TIP4P/OPLS model. For $M = Na$, the global minimum is not a cage and not ion centered, the best (distorted) dodecahedral cage structure is also not ion centered and energetically clearly disfavored. For $M = K, Cs$, distorted dodecahedral cages are formally the global minima, but qualitatively different structures are local minima with almost the same energy (not a cage for $M = K$, and not only five-rings for $M = Cs$).

Above, we mentioned that anions such as Cl^- or larger cations such as Cs^+ exhibit a tendency for surface solvation in theory and experiment, even in the smallest clusters, while other cations such as Na^+ prefer centered structures.^[222] Part of this phenomenon is simply a result of ion size. For the alkali cations,^[221, 246] where the polarizability of the cation is not important,^[224] already the simple TIP4P/OPLS model (without explicit polarizabilities) reproduces this behavior: the Na^+ ion does not show any surface solvation structures. Some of the corresponding K^+ ion solvation cluster structures are already more closely related to the Cs^+ ion cluster. In the Cs^+ ion clusters the Cs^+ ion itself is at the surface of such clusters, even for very small cluster sizes, and is completely enclosed by a solvent hull only at size $n = 18$, shortly before the occurrence of the distorted dodecahedral “clathrate” cage at $n = 20$. Figure 16 indicates these effects, by comparing the global minimum energy structures of these cation micro-solvation clusters for $n = 4$. This phenomenon can be described as a structural transition from ion-centered forms to surface forms, with increasing ion size. For halogen anions^[201, 203, 204, 247–250] it is tempting to draw a similar conclusion, since Cl^- and larger anions clearly prefer surface solvation, whereas centered structures can compete with surface structures only for the smaller F^- ion. The cited

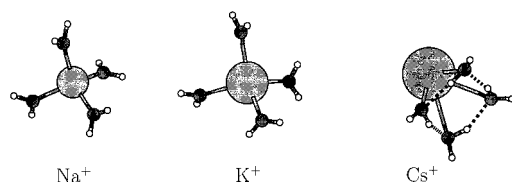


Figure 16. Global minimum energy structures^[246] of $M^+(H_2O)_4$, $M = Na, K, Cs$, for the empirical TIP4P/OPLS model. For $M = Na, K$, the clusters are ion centered, for $M = Cs$ the structure corresponds to surface solvation. For larger clusters, some best $M = K$ structures have more similarity with the corresponding $M = Cs$ structures.

sources agree, however, in ascribing this effect not just to the size of the ion but also to its polarizability (which is also related to the size).

4. Summary and Conclusions

In this article, several different cluster systems were presented. For each of these systems, characteristic transitions in structure (and other properties) as a function of cluster size (and also as a function of other factors) were diagnosed: Already for the simplest possible system, the LJ clusters, there is a surprising variety of structures, with (at least?) four different basic structural types, which are in close competition. For small and medium-sized LJ clusters, amenable to global geometry and MD or MC treatments, the icosahedral form wins almost always (except for very few isolated cluster sizes, between geometrical shell closures), as expected from the simple packing argument. From this trend, one can tentatively conclude that the deviation from hard-sphere behavior described by the LJ potential still is a relatively small perturbation. Icosahedral order, however, cannot survive all the way to the periodic crystal; this can be shown by the impossibility of fivefold rotation axes in the crystal, but also by alluding to different strains found for the different structural types (that is, with pair distances deviating from the minimum of the pair potential, induced initially by the “frustration” of the system in three-dimensional space). As yet this is only a qualitative description that does not permit predictions of cluster sizes where structural transitions actually occur. Strain in this classical LJ system is relatively small; thus the transition away from icosahedral structures occurs at clusters of such a large size that it could not yet be located reliably, neither by global geometry optimizations nor by MD or MC simulations. The higher strain in molecular van der Waals clusters, however, shifts this transition to much smaller cluster sizes which can be treated by these methods. If one varies the well width of the LJ potential (for example by substituting it with a Morse potential with different width parameter) but still stays with simple pair potentials of this general form, the basic structural types do not change, but the dominance of the icosahedral form can be lost completely by suitable choices of the well width. This result can again be understood by a strain argument: variation of the well width is nothing but variation of the energy difference to the pair potential minimum at a given deviation from the optimal pair distance. This, in turn, is nothing but a variation of the size of

the contribution of strain energy to the total energy, and this leads to different preferences for the different structural types, because of their different strain.

Upon leaving such simple prototypical clusters for more “chemical” systems—silicon was taken as example in this article—isotropic pair interactions cease to be a good approximation; many-body terms have to be added to describe directed covalent bonds or preferences for planarity. Clearly, this leads to new structures that cannot be explained by simple packing or strain arguments anymore. Nonetheless we again do not find just one dominating cluster structure but structural transitions as a function of cluster size. For a few systems it has been possible to arrive at a well-founded set of simple rules to describe and perhaps even understand the various possible cluster structures, as was demonstrated for phosphorus by Marco Häser and Stephan Böcker.^[251] However, these remain isolated islands of understanding; others will be added in the future. System-independent general rules would be still more interesting, but we do not yet see the beginning of a development in this direction.

Another possible parameter to vary is the type of chemical bonding. As shown here for the example of mercury clusters, there are links between cluster size, bonding character, and cluster structure. But actual structures found seem to be more complicated than expected from the current picture of changes of bonding character with cluster size. For clusters of relevant size, the highly accurate *ab initio* calculations and global geometry optimizations or MD/MC simulations necessary for a better understanding are still too expensive, even today.

The transition from atomic to molecular clusters is not trivial, since the difficult problem of an exponentially increasing configuration space of particle positions in the cluster is augmented by an also exponentially increasing search space of particle orientations. “Steps” (in iterative optimizations, or in MD/MC simulations) in these two spaces have a strong influence on each other, thus these two spaces are not separable. Therefore, it comes as no surprise that the cluster size region amenable to theoretical treatment of molecular clusters is about one order of magnitude smaller than that of atomic clusters. Nevertheless, in some cases it was possible to find characteristic structural transitions even in such a reduced size region, for example, in the system of pure, neutral water clusters the theoretically and experimentally fairly well investigated transition from quasiplanar to three-dimensional structures near $n=6$ or the currently neither theoretically nor experimentally locatable transition from all-surface structures to clusters with at least one molecule in the interior. To a much larger degree than for the transitions mentioned above, it is immediately clear here that these structural transitions have to occur; but a more detailed understanding of the actual reasons for occurrence of these transitions at certain cluster sizes is still lacking completely.

As a final source of complication, we mentioned heterogeneous clusters, consisting of more than one species. Clearly, we have still more parameters to vary here, namely the relative distribution of the species in the cluster and the relative properties of the species (size, charge, polarizability, etc.). Changes in these parameters can again induce charac-

teristic structural transitions in these clusters, as was demonstrated here with microhydration clusters of simple ions as an example. Again, also in this area, investigations are just starting.

Even if structural transitions in clusters are the rule rather than the exception (and perhaps even have to occur), and even if some structures appear in seemingly different systems (for example, icosahedral forms in van der Waals clusters and metals, or the tetracapped trigonal prism for Si_n and Hg_n), most of the basic questions mentioned in the introduction are still unanswered: Do structural transitions occur according to universal laws, or do they solely depend on the particular system (or potential)? One type of universal law has been known for a long time, namely the simple packing argument (at the level of hard spheres), and the strain argument for LJ clusters may turn into another universal law for van der Waals systems. But we still do not even begin to understand how packing, strain, and potential interact for more complicated potential forms (for example, with directed covalent terms) and what happens if the balance between these factors is changed. Clearly, we are still in a phase of accumulating empirical details and observations for various systems, as also done in this article.

Therefore, many old, basic questions are still open, for example, which potential form leads to which cluster structures and structural transitions? How can one deduce interactions between particles from experimentally observed structures and structural transitions (and perhaps magic numbers)? In a recent publication,^[252] new universal connections between the potential surface and the potential function were discovered by catastrophe theory, but we still have a long way to go before we can answer these questions for clusters.

In a similar way, the connections of this field to its immediate neighbors also need further investigation. What is the actual importance of the largely static diagnoses of cluster structure transitions made here for the dynamics of cluster growth and for seed growth in crystal formation? Can we expect complete changes of cluster structure at structural transition sizes, or are seemingly optimal small seeds always dead ends because of their ultimately wrong structure, and the successful seeds are those that start their growth already in the correct bulk structure? Or is all this too idealized anyway, and seeds with a wrong structure end up as faults in the crystal?

Increasing computer power and more efficient implementations of theoretical approaches will permit simulations of structural transitions in clusters with an increasing amount of detail, in my opinion this will not necessarily also lead to understanding. This general problem also occurs in many other realizations of many-body problems in the natural sciences, for example in weather prediction, traffic dynamics, or in artificial and natural neural networks (brains). A detailed description on a microscopic level has become possible, but the actual many-body phenomena still seem elusive, because our understanding has to occur on a less detailed level. From this, it follows that we may have a better chance to increase our understanding if we manage to introduce intermediate levels with less detailed descriptions. In the cluster structure problem discussed here, one possible

candidate could be a suitably generalized three-dimensional packing problem, with larger and partially flexible building blocks, the inner properties of which are determined in advance by (ab initio) calculations but then neglected.

I thank the Aventis Foundation for a Karl-Winnacker scholarship. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

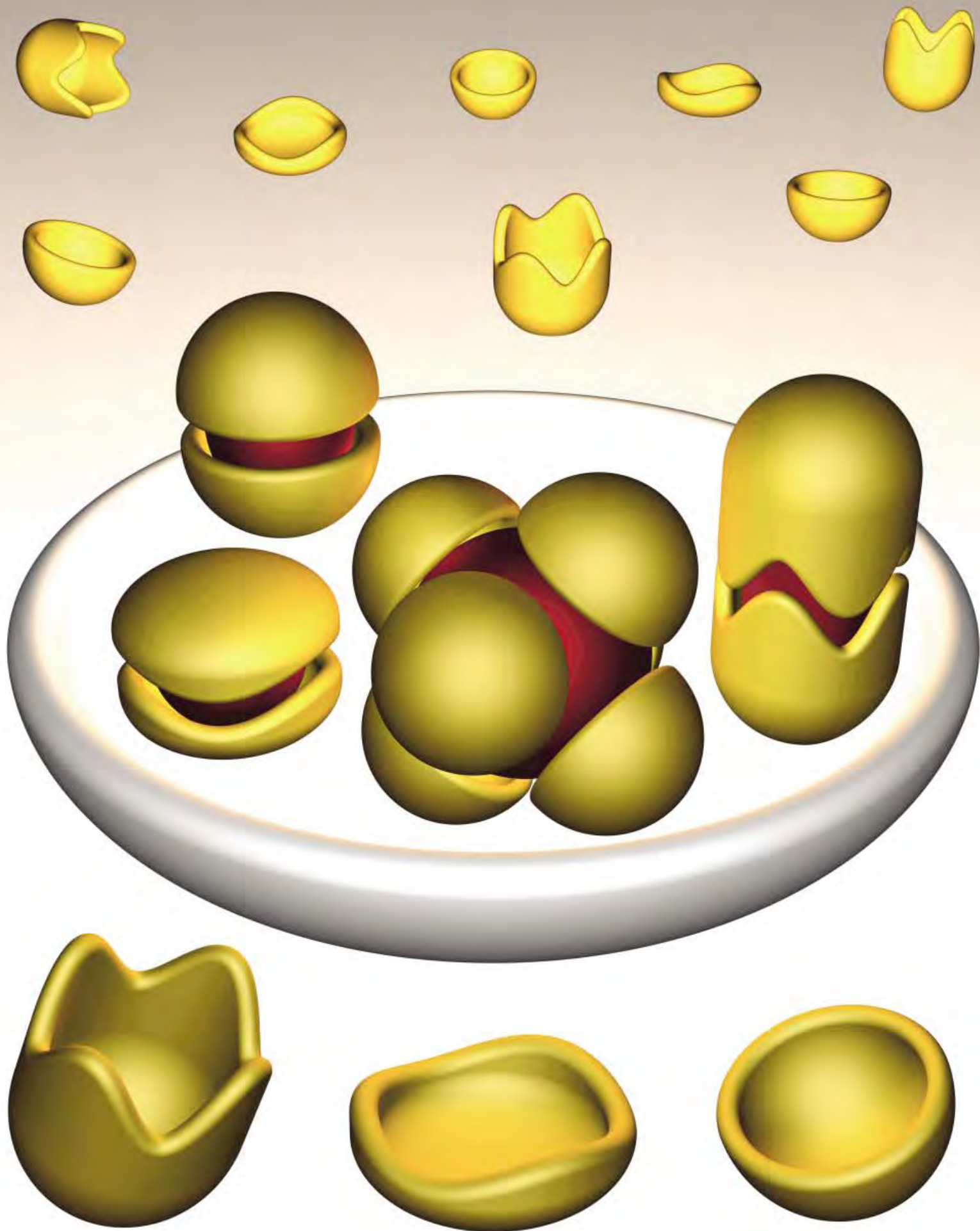
Received: October 29, 2001 [A498]

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Molecular Encapsulation

Fraser Hof, Stephen L. Craig, Colin Nuckolls, and Julius Rebek, Jr.*

Dedicated to Ivar Ugi

Louis Kahn, architect of the Salk Institute in La Jolla, said^[1] “even a common, ordinary brick wants to be something more than it is.” Suppose that were also true of molecules. We know that they can and do aggregate; they give complex structures, and by doing so they acquire new properties—functions that may not be apparent from a study of the individual compo-

nents. This review is about molecular aggregates of a certain sort, namely, those that assemble and more or less completely surround other molecules. Taking part in this intimacy imparts unique properties to the participants, and new functions emerge from the aggregate as a whole. For the most part, we emphasize self-complementary structures. Their ability to assem-

ble—an expression of the molecule’s desire to be something more than it is—results from instructions engineered into the molecules during their creation.

Keywords: host–guest systems • molecular capsules • molecular recognition • self-assembly

1. Introduction

In the 1980s, most of the publications on molecular recognition dealt with the selectivity of synthetic receptors and the energetics of intermolecular forces, and were confined for the most part to bimolecular systems. Termolecular systems would show up in a desultory way, such as in models for allosteric effects,^[2] but there was much less work in pursuit of, for example, binding cooperativity.^[3] There were rare cases in which a third molecule would interact with a weakly held bimolecular complex, and their beauty was exhilarating—like hitting a moving target.^[4]

Studies of termolecular systems spread quickly during the 1990s in the form of template effects.^[5–7] Interest in molecular self-replication had been ignited by von Kiedrowski^[8] using nucleic acid components and the fire leapt to modified nucleic acids^[9, 10] and entirely synthetic systems.^[11–14] Even peptides now fan these flames.^[15, 16] Elsewhere, other bimolecular

reaction templates were devised^[17] and more complex systems were contrived. This is engineering (or is it art?)^[18] at the molecular level.^[19] It did not matter that these systems weren’t particularly efficient, what mattered was that they improved the understanding of three-component systems.

Synthetic receptors became more sophisticated and concave surfaces such as clefts,^[20] armatures,^[21] tweezers,^[22, 23] bowls,^[24] and other shapes^[25] emerged for the study of reversible interactions. We thought that a receptor could be created that could completely surround the target by using only the weak intermolecular forces of molecular recognition. These systems would be capsular assemblies, the reversible counterparts of the carcerands and cryptophanes—the covalently bound “molecules within molecules” crafted by Cram et al.^[26] and Collet and co-workers.^[27] The synthetic economy of using aggregates of self-complementary compounds^{[28–30][31]} rather than one large molecule as a receptor proved irresistible. These structures have been termed “encapsulation complexes” and they are now tools of physical organic chemistry on the nanoscale.

At the outset, most of the assemblies—spectacular as they were in the number of components, the intricacies, and sheer molecular weight—did little more than fill space. More sophisticated properties quickly emerged, and these will be the focus of this review. The complexes are used today as probes of isolated molecules and of the intrinsic characteristics of the liquid state, and are capable of enantioselective recognition, reversible polymerization, isolation of reactive species, and promoting reactions within their interiors.

[*] Prof. J. Rebek, Jr., F. Hof

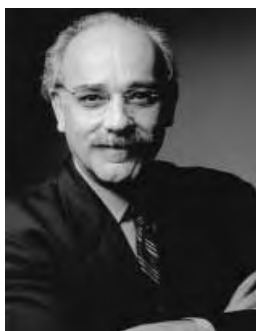
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2876
E-mail: jrebek@scripps.edu

S. L. Craig
Department of Chemistry, Duke University
Durham, NC (USA)
C. Nuckolls
Department of Chemistry, Columbia University
New York, NY (USA)

Solvent-free environments provide an undiluted, often intensified interaction between the host and guest or between multiple guests themselves. Groups of molecules residing in the channels of zeolites, the pores of polymers, active sites of enzymes, and within globular micelles or dendrimers display behavior that is amplified by their environment. Encapsulation is a means by which the environment and encounters of a *single* molecule can be rigorously controlled. What can be learned about them in their isolated states, either alone or, as we shall relate, grouped in pairs? Much effort has been expended on isolation tactics in the chemical sciences. In the solid state or glassy states, inert matrices are used at low temperatures to isolate and stabilize reactive intermediates. In the gas phase, isolation can be achieved by subjecting a

molecule to such low pressure that collisions with other molecules are essentially zero.^[32] In the encapsulation complexes presented in this review, molecules are isolated from solvent encounters at ambient temperatures in the liquid phase.

Other supramolecular structures are also capable of surrounding guest molecules. The differences here are those of topology and timing. Supramolecular rings, tubes, and cavitands are able to briefly bind one or more guest molecules within a restricted environment, while still allowing varying amounts of solvent access to the secluded guests. We will not dwell on these here; rather, this review focuses on hosts that self-assemble and encapsulate molecules within a closed-shell topology.



J. Rebek, Jr.



F. Hof



S. Craig



C. Nuckolls

Julius Rebek, Jr. was born in Hungary in 1944 and lived in Austria from 1945–1949. He and his family then settled in the USA in Kansas. He received his undergraduate education at the University of Kansas in 1966, and obtained his Ph.D. degree from the Massachusetts Institute of Technology (1970) for studies in peptide chemistry with Professor D. S. Kemp. As an Assistant Professor at the University of California at Los Angeles (1970–1976) he developed the “three-phase test” for reactive intermediates. In 1976 he moved to the University of Pittsburgh where he rose to the rank of Professor of Chemistry and developed cleftlike structures for studies in molecular recognition. In 1989 he returned to the Massachusetts Institute of Technology, where he was the Camille Dreyfus Professor of Chemistry, and devised synthetic, self-replicating molecules. In July of 1996, he moved his research group to The Scripps Research Institute to become the Director of The Skaggs Institute for Chemical Biology, where he continues to work in molecular recognition and self-assembling systems.

Fraser Hof was born in Medicine Hat, Alberta, Canada. He obtained a B.Sc. in chemistry at the University of Alberta in 1998, and is currently pursuing a Ph.D. under the direction of Professor Julius Rebek, Jr. at the Scripps Research Institute in La Jolla, California. He has been awarded postgraduate fellowships by the Natural Sciences and Engineering Research Council of Canada and the Skaggs Institute for Chemical Biology. His research focuses on the rational design of novel emergent properties through supramolecular chemistry.

Stephen Craig received his undergraduate degree in chemistry at Duke University, Durham (1991) and obtained an M.Phil. degree from Cambridge (1992) and a Ph.D. from Stanford University (1997). After two years as a Research Chemist in DuPont Central Research, he went to Scripps Research Institute in 1999 where he was an NIH postdoctoral fellow in the lab of Professor Julius Rebek. He joined the Duke chemistry department in 2000 as an Assistant Professor, where his research interests center around the physical organic chemistry of materials.

Colin Nuckolls joined the faculty of Columbia University as an Assistant Professor of organic chemistry in July 2000. His group is studying the properties of materials that form through self-assembly. Previously, he was a National Institutes of Health post-doctoral fellow in the laboratory of Professor Julius Rebek, Jr. at the Scripps Research Institute. His undergraduate degree was awarded from The University of Texas, Austin where he worked with Professor Marye Anne Fox. He obtained his doctoral degree from Columbia University where he studied under the tutelage of Professor Thomas Katz.

Molecules that form supramolecular capsules are defined by two fundamental emergent properties: self-assembly and the encapsulation of guest molecules. Self-assembly is based on capsule components bearing complementary functional groups capable of reversible, noncovalent interactions. The noncovalent forces that are useful in constructing capsules are primarily hydrogen bonds and metal–ligand interactions. Both enjoy facile reversibility and reliable directionality, but hydrogen bonds offer greater plasticity and faster equilibration, while metal–ligand bonds typically offer greater strength and more rigidity. High-symmetry designs are used to multiply these individually weak and reversible interactions into coherent structures with lifetimes that range from microseconds to hours. The subsequent encapsulation of guest molecules is dependent on the complementarity of the guest's size, shape, and chemical surface with the cavity of the host. The filling of space within the host is of utmost importance: nature abhors a vacuum, and this would seemingly include even those vacuums that measure only 10^{-25} liters!^[33]

Although these capsules are constructed with the express purpose of isolating guest molecules from the bulk solvent, the role of solvent in the formation of the capsules cannot be ignored. The medium must not disrupt the interactions that hold the components of the capsule together. Capsules constructed through metal–ligand interactions are typically disrupted by strongly ligating solvents, while they may remain stable in water. In contrast, solvent competition for hydrogen bonds prevents capsules constructed using these forces from being stable in aqueous media. The space-filling properties of the solvent must also be considered when dealing with encapsulation complexes. While the encapsulation of the solvent itself is sometimes desirable, the use of a large solvent that is physically excluded from the cavity can be an important tactic when encapsulating other guest molecules.^[34]

2. Structural Motifs for Encapsulation

2.1. Glycoluril-Derived Hydrogen-Bonded Capsules

Glycoluril has been used to spectacular effect in the construction of supramolecular systems.^[35] A more detailed discussion of the guest-binding properties of self-assembling glycoluril-based capsules than that which follows can be found in a recent review.^[36]

Reversibly formed molecular capsules began with the “tennis ball”, **1** (Figure 1a). The monomer (**2**) consists of two glycoluril subunits appended to a central aromatic skeleton; the glycoluril units provide curvature and a self-complementary hydrogen-bonding motif. The tennis ball is held together by eight hydrogen bonds, and as a host structure has a tiny cavity capable of housing guests with a volume of about $50 \text{ \AA}^3$. Accordingly, the tennis ball includes methane, ethane, ethylene, and the noble gases, while larger guests such as propane, allene, and isobutylene are excluded.^[37, 38] Variation in the spacer leads to smaller^[39] and larger capsules (“softballs”, **3**, Figure 1b).^[40–42] The same general symmetry remains, but apart from binding larger guests, the “softballs”

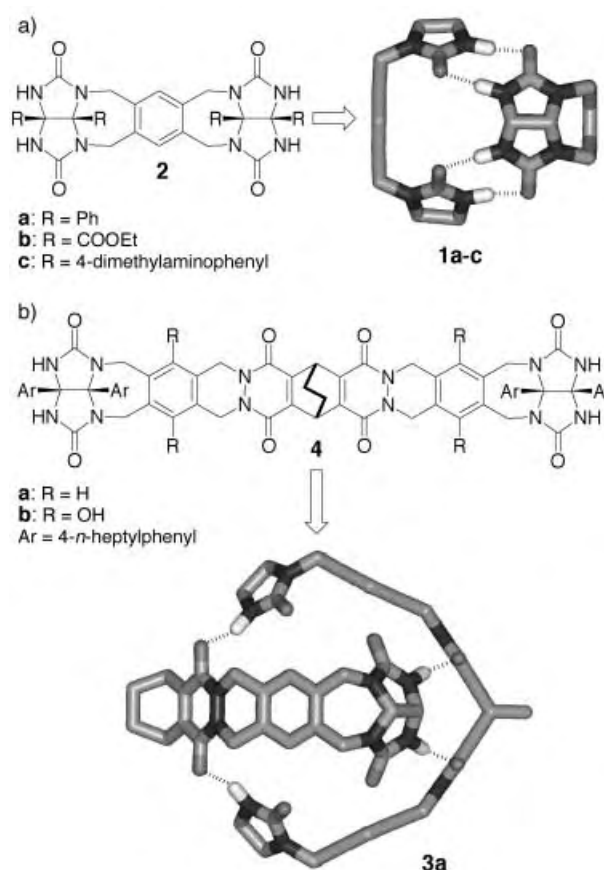


Figure 1. Self-assembling glycoluril-based dimeric capsules: a) the “tennis ball” and b) the “softball”. As in most hydrogen-bonded capsules, curved monomers and self-complementary hydrogen-bonding seams are necessary components of the capsule geometry. (Some substituents and hydrogen atoms have been omitted for clarity.)

(their internal volumes lie between 240 and $320 \text{ \AA}^3$) are also capable of simultaneously binding *two* copies of moderately sized guests such as benzene.^[41] Glycolurils were also appended to spacers of threefold symmetry to form small, rigid (**6**, Figure 2a)^[43] and large, flexible capsules (**8a** and **b**, Figure 2b).^[44]

Cyclic sulfamides share the self-complementary hydrogen-bonding patterns of glycolurils. However, given the opportunity, sulfonamides and glycolurils prefer heteromeric hydrogen bonds. That is, they attract each other rather than themselves. A monomer such as **9** that contains both functional groups is programmed for self-assembly: if the groups appear at the ends of a suitably curved structure, assembly proceeds in a head-to-tail manner, with the best hydrogen donors and acceptors in contact.^[45] The result is a capsule (**10**) made up of four subunits surrounding a cavity with a volume of about $160 \text{ \AA}^3$ (Figure 3a).^[46] The entropic penalty of bringing together four monomers and one guest in a single, discrete complex is forfeited by the enthalpic gains provided by the formation of 16 hydrogen bonds and whatever host–guest interactions are on offer. As with the dimers, the tetrameric capsules bind molecules on the basis of size, shape, and chemical functionality. The larger monomer **11** assembles into the tetrameric capsule **12** (Figure 3b) that encapsulates

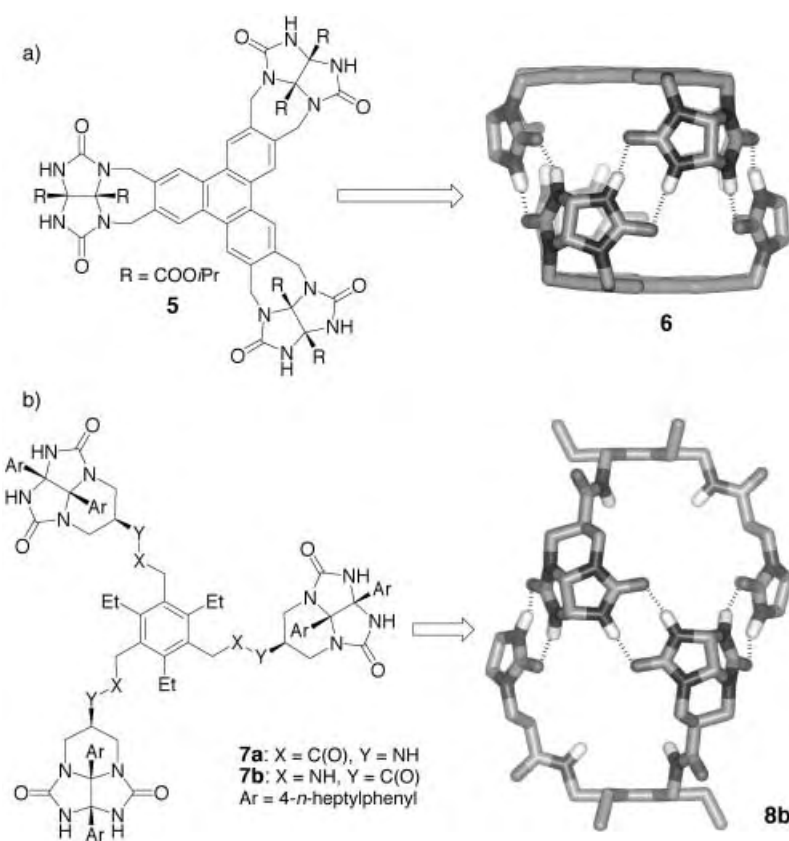


Figure 2. C_3 -symmetric self-assembling glycoluril-based dimers: a) the “jelly donut” describes a flattened cavity. b) Capsule **8b** contains holes through which small guests may pass freely. (For clarity here and in the following Figures, only hydrogen bonds in the foreground are depicted and some substituents and hydrogen atoms have been omitted.)

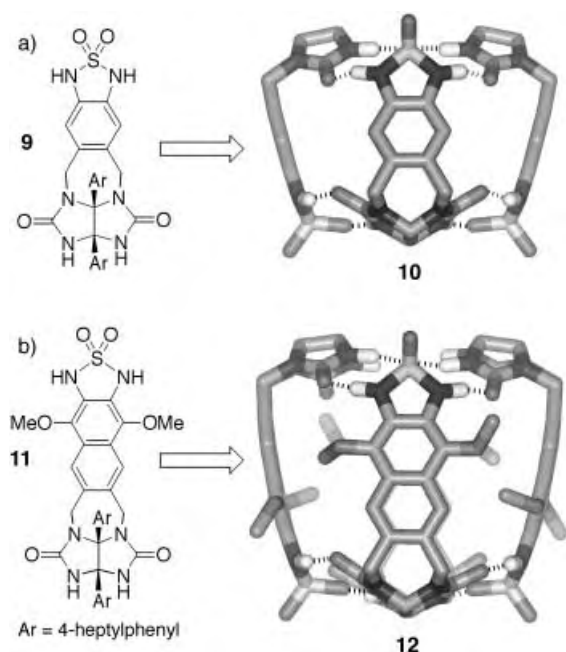


Figure 3. Self-assembling tetrameric capsules. Two seams, each comprised of eight hydrogen bonds, stitch together a total of four identical monomers in a head-to-tail manner.

guests as large as the natural product longifolene within its expanded cavity (about $270 \text{ \AA}^3$).^[47]

2.2. Cyclophane-Based Hydrogen-Bonded Supramolecular Capsules

Calix[4]arene and resorcin[4]arene are much admired, even standard subunits of self-assembled capsules. Both molecules exhibit variable conformations that can, through appropriate derivatization, be fixed into a single bowl-shaped conformation. The concave face of a bowl represents one half of a closed-shell topology, and a variety of functional groups mediate the corresponding dimerization. We refer the reader to a recent review^[48] for a more detailed discussion of calixarenes than that which follows.

Secondary ureas were installed on the upper, wider rim of a calix[4]arene. In the presence of an appropriate guest molecule the ureas from two such calixarene monomers interdigitate and organize a directional seam of 16 hydrogen bonds around the equator of a dimeric capsule (**14**, Figure 4).^[49] A variety of aromatic, aliphatic, and cationic guests are held within the twisted, bipyramidal cavity of approximately $180 \text{ \AA}^3$. The distal urea nitrogen atoms can be easily adorned with a variety of functional groups that alter the self-organizing behavior of the calix[4]arene monomer.^[50, 51] This modularity programs heterodimeric assemblies (**13a,b**),^[52] kinetic stability (**13c,d**),^[53] and chirality (**13e**)^[54, 55] into the monomers. Larger calix[6]arene capsules have also recently been reported.^[56]

The bowl shape of calixarenes and resorcinarenes led to other versions, inspired by the report by MacGillivray and Atwood of a spectacular hexameric capsule in the solid state.^[57] The structure shows a chiral arrangement of six resorcinarene subunits (**15a**) enclosing an

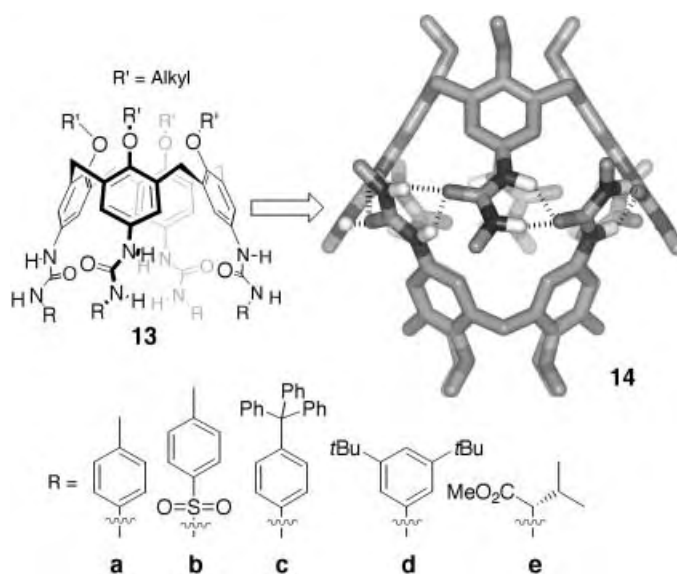


Figure 4. Self-assembling calix[4]arene tetraureas. The formation of homodimers (for example, $\mathbf{13a} \cdot \mathbf{13a} = \mathbf{14a}$) and heterodimers (for example, $\mathbf{13a} \cdot \mathbf{13b}$) is determined by the identity of the urea substituents on the basis of electronic or steric properties.

enormous cavity of about $1375 \text{ \AA}^3$ (Figure 5). The hexameric capsule **16a** features a total of 60 hydrogen bonds, in which 8 ordered water molecules are recruited to integrate the architecture. A similar water-bridged spherical structure was indicated by the ^1H NMR spectrum of **15b** in benzene, but no evidence of specific guest encapsulation by the cubic hexamer **16b** was reported. A hydroxy derivative, also a hexameric assembly in the solid state, also did not give any clues as to what was trapped inside.^[58]

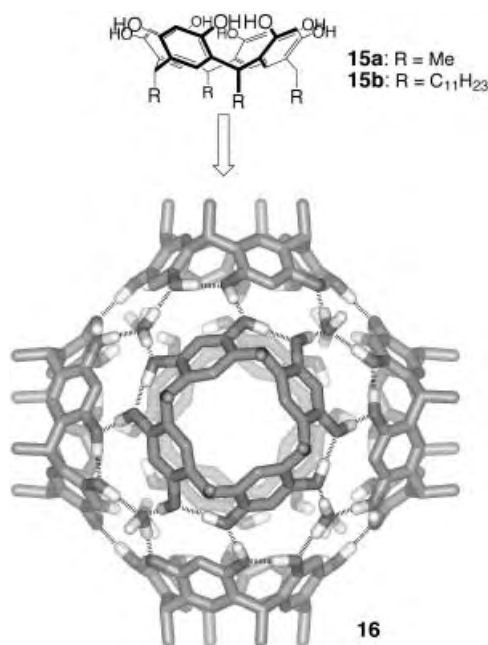


Figure 5. Hexameric structure observed in the solid state for methyl-substituted resorcin[4]arene **15a**. Eight water molecules are included in the hydrogen-bonding seam. Soluble monomer **15b** also forms this structure in solution in the presence of appropriate guests.

We revisited the solution characteristics of the resorcinarene monomer **15b** (Figure 5) more than a decade after Aoyama et al. had described the formation of 1:1 complexes of **15b** with dicarboxylic acids in CDCl_3 solution and subsequently with ribose, terpenes, and even steroids.^[59] We found kinetically stable complexes of **15b** formed in wet CDCl_3 when suitable guests were available.^[60] Guests such as large tetraalkylammonium and tetraalkylphosphonium salts reveal complexes with a host:guest ratio of 6:1. The dependence on the guest size correlates nicely with the expected cubic hexameric structure observed by MacGillivray and Atwood in the solid state. Additional evidence suggests that the charged guests are encapsulated as ion pairs. When tetrabutylammonium bromide acts as the guest, enough space remains to concomitantly encapsulate a secondary neutral guest such as 4-phenyltoluene, thus three different species occupy the cavity. In the solid state, water-bridged dimeric capsules of **15** with small alkyl ammonium guests were characterized by Murayama and Aoki^[61] as well as Rissanen and co-workers.^[62, 63]

Following the synthetic and structural work of Cram et al.^[26] and Dalcanale and co-workers,^[64, 65] we devised and

synthesized **17**, in which a vase-shaped cavitaand structure presents four imide functions around its rim (Figure 6). The molecule dimerizes through bifurcated hydrogen bonds to form a capsule (**18**) about the size of a can of tennis balls (the molecular sort, see Figure 1a).^[66] The nonspherical shape of the cavity accommodates elongated guests and also promotes

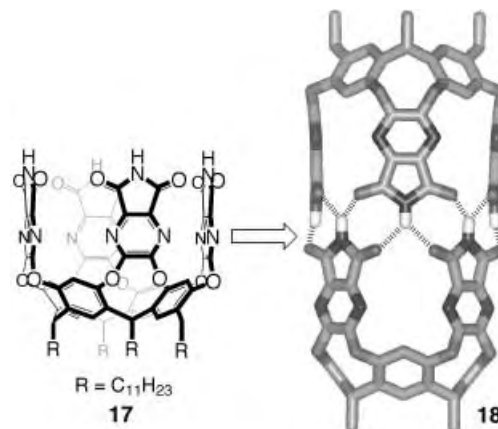


Figure 6. Self-assembly of an imide-substituted cavitaand into a dimeric capsule capable of binding elongated guests.

the pairwise selection of two simple aromatic compounds in an edge-to-edge manner. The selection depends strongly on the shape and size of each guest. Two molecules of benzene or two molecules of toluene are encapsulated simultaneously, while two molecules of *p*-xylene are not. In the presence of benzene, toluene, and *p*-xylene the capsule shows a strong (about 20:1) bias for the simultaneous binding of a benzene:*p*-xylene guest pair over the constitutionally isomeric toluene:toluene pair. Although the origin of this preference is not known, it demonstrates the stunning selectivity of molecular capsules.

Other resorcinarene platforms have also been developed. Chapman and Sherman explored the use of ionic hydrogen bonds in the generation of self-assembled capsules using a partially deprotonated hydroxy-substituted resorcinarene (**19**, Figure 7a).^[67] Kobayashi et al. have constructed a similar methylene-bridged resorcinarene scaffold functionalized with four carboxylic acids (Figure 7b).^[68] Here, 2-aminopyrimidine is used as a wedge-shaped hydrogen-bonding bridge that forms two hydrogen bonds with each of two carboxylic acids on neighboring molecules (**20**). Resorcinarene **21**, which employs hydroxy and ester functional groups as hydrogen-bonding donors and acceptors, respectively, allows the assembly of supramolecular capsule **22** (Figure 7c).^[69] Flexible electron-rich walls are able to collapse and form good contacts with a π -acceptor guest, which results in a dimeric capsule that binds a tropylium cation within its cavity. The glycoluril module^[44] and resorcinarene module have been hybridized in the supramolecular capsule **24** (Figure 8).^[70] The large interior volume (about $950 \text{ \AA}^3$) allows for the “host within a host” supramolecular encapsulation of ionic cryptate complexes, an arrangement analogous to Russian matryoshka dolls.

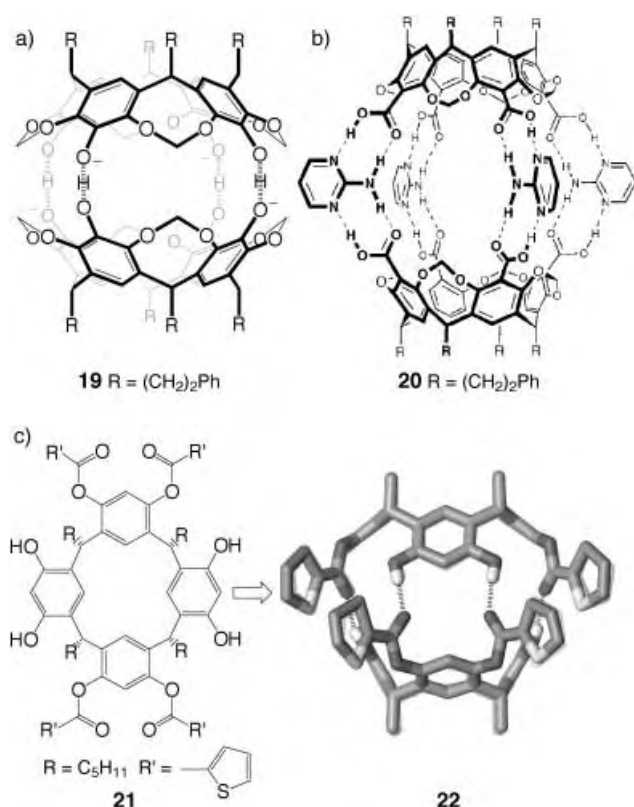


Figure 7. Dimeric molecular capsules based on resorcin[4]arene building blocks: a) a dimeric capsule stitched together by charged hydrogen bonds, b) a capsule utilizing 2-aminopyridine as a hydrogen-bonding wedge (reprinted with permission from ref. [69]), c) the flexible walls of this resorcinarene collapse to give π contacts with encapsulated guest.

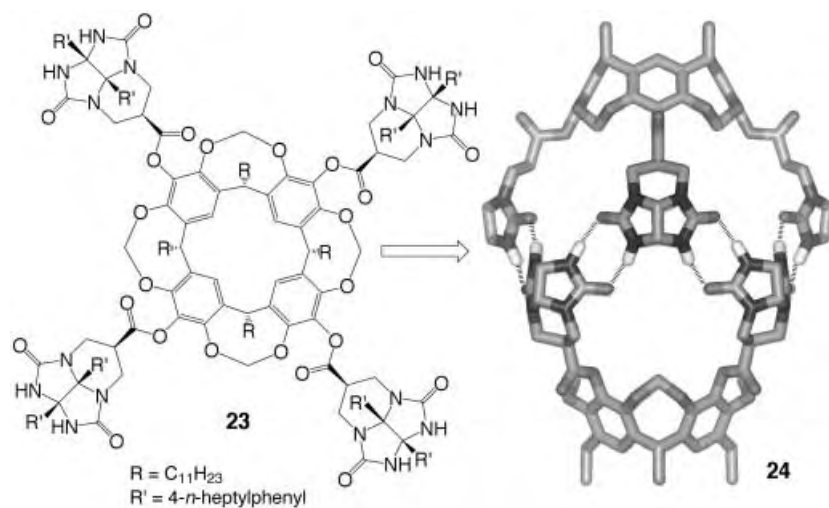


Figure 8. Self-assembly of a resorcin[4]arene-glycoluril hybrid capable of encapsulating ion-cryptate complexes.

2.3. Cyclophane-Derived Metal-Ligand-Based Supramolecular Capsules

Hydrogen bonds do not have exclusive rights to the assembly of supramolecular capsules, and molecular housings built by using metal-ligand interactions have their own architectural style.^[71] Whereas the rectilinear arrangement of

ideal hydrogen bonds requires molecules with curvature elsewhere, in the metal-ligand assemblies metal hinges can be installed in the corners while the walls are constructed from flat ligand panels. Dalcanele and co-workers have created a variety of bridged resorcinarenes functionalized with four nitrile groups for the purposes of metal-ligand-directed self-assembly.^[72–74] Square-planar palladium or platinum complexes having two labile ligands in adjacent positions can act as coordinating corner units for the self-assembly of such nitrogenous ligands. The resulting metal-ligand interactions (and the assemblies that they generate) are reversible and robust in a variety of solvents. The combination of a C_{4v} -symmetric resorcinarene-nitrile ligand and a right-angle metal subunit in a 1:2 ratio leads to the formation of a self-assembled supramolecular cage complex **25** (Figure 9a). The complex bears a total +8 charge, and the cavity is found to encapsulate one of the eight counterions. The assembled structure is stable in water, but is subject to decomposition by competing ligands such as triethylamine or acetate.

Shinkai and co-workers have demonstrated that the substitution of pyridines into calix[4]arenes also results in the self-assembly of supramolecular capsules. A rigidified calixarene monomer displaying four pyridine ligands undergoes metal-directed self-assembly to produce capsule **26** (Figure 9b) in a manner analogous to that of **25**.^[75] The bridging glycol substituents at the lower rim stabilize the C_{4v} -symmetric cone conformation necessary for assembly. Modification of a homooxalix[3]arene derivative to include 4-pyridyl groups gives a species that undergoes metal-directed self-assembly to form a supramolecular capsule (Figure 9c).^[76]

This assembly (**27**) even encapsulates [60]fullerene ($K_a = 54 \text{ M}^{-1}$).

The list of metal ions useful for directing encapsulation continues to grow. Harrison and co-workers introduced tridentate chelating ligands as structural elements. A resorcinarene functionalized with four iminodiacetate groups (**28**) shows an affinity for binding Co^{II} , Cu^{II} , and Fe^{II} salts. The result is the complexation of each metal in a chelated pseudo-octahedral environment and the generation of supramolecular capsules **29** (Figure 10).^[77–80] They are stable in water and encapsulate a wide variety of organic compounds, such as cyclic and acyclic aliphatic alcohols, ethers, ketones, esters, and halides, within a cavity of approximately $215 \text{ \AA}^3$. Compounds held in close contact with the metals that line the cavity experience enormous paramagnetic shifts. Guests encapsulated within the Co^{II} complex show upfield chemical shifts of 18 to 40 ppm upon complexation.^[80]

The water-soluble *p*-sulfonatocalix[4]arene **30** is even more impressive in its response to small ligands and metals. It is coaxed to assemble by the presence of 1 equivalent of pyridine *N*-oxide and 0.5 equivalents of $\text{La}(\text{NO}_3)_3$.^[81] The resulting spherical cluster (**31**, Figure 11) has a delicate balance of hydrogen bonds, van der Waals forces, metal-ligand interactions, and electrostatic contacts that work in

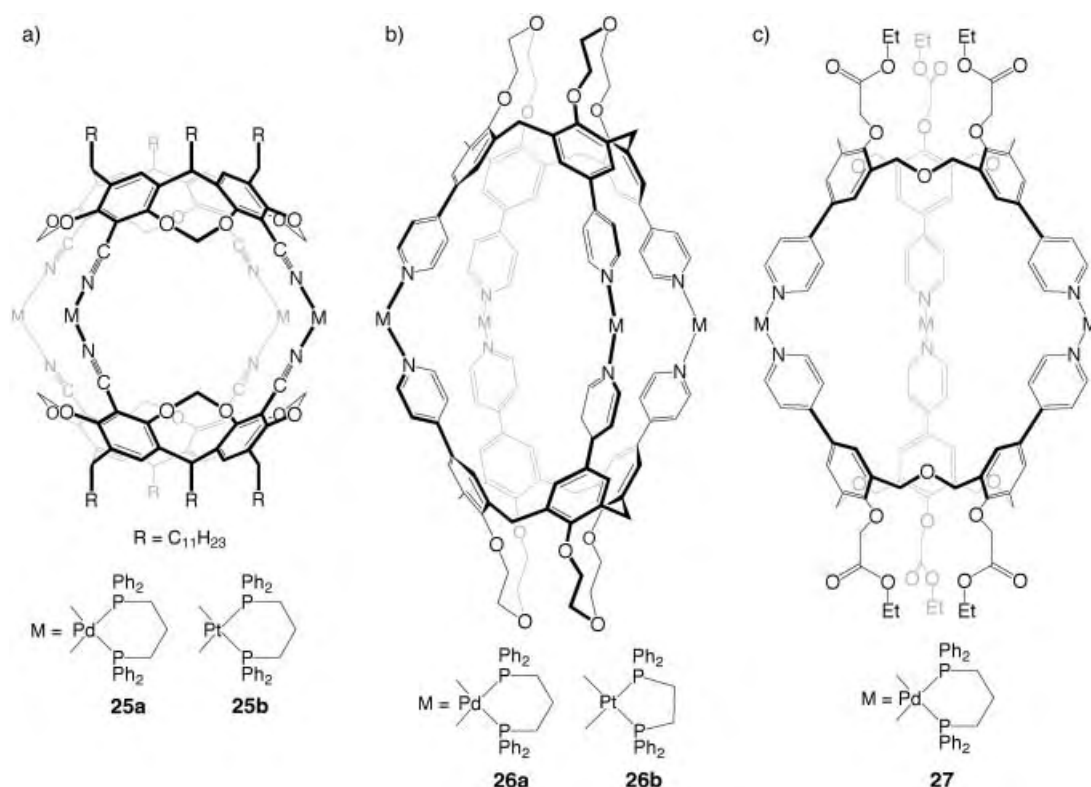


Figure 9. Metal-mediated dimerization of cyclophane-based ligands to form supramolecular capsules.

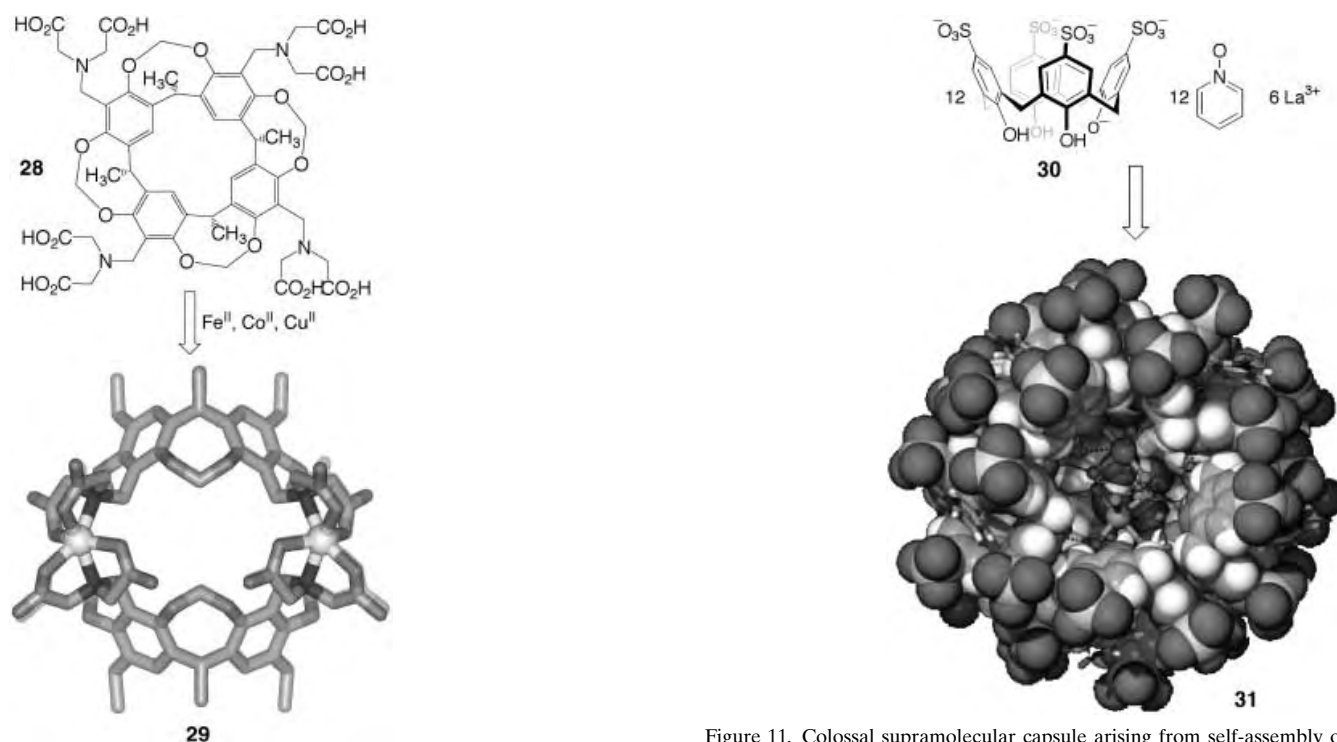


Figure 10. Dimerization of a cyclophane bearing four tridentate ligands mediated by four metal ions in pseudo-octahedral environments.

concert to create an ordered supramolecular capsule. X-ray crystallographic analysis shows: 1) 12 calixarene units functioning as pyramidal wedges, 2) a pyridine *N*-oxide molecule filling the cavity of each calixarene, and 3) the lanthanide ions

Figure 11. Colossal supramolecular capsule arising from self-assembly of 12 calix[4]arene subunits, 12 copies of pyridine *N*-oxide, and 6 La³⁺ ions. One calix[4]arene subunit has been omitted to allow visualization of the capsule interior, which is occupied by 2Na⁺ ions and 30 ordered water molecules. (Reprinted with permission from ref. [81].)

acting as coordinating hinges between calixarenes of adjacent clusters. The internal cavity of this spherical assembly has a prodigious volume of about 1700 Å³, and is occupied by an

ordered cluster of 2 sodium ions and 30 water molecules. On the scale of the other capsules, this resembles a soccer ball. Under a different stoichiometry, the same three subunits can also form open-ended helical tubes in the solid state.^[81]

2.4. Complexes Based on Tris(pyridine) and Tris(pyrimidine) Ligands

In a dramatic departure from cyclophane-based capsules, Fujita et al. have used simple triangular heterocyclic ligands (Figure 12) in combination with *cis*-enforced square-planar Pd and Pt complexes for the construction of highly symmetric supramolecular capsules.^[82] The positively charged metal centers impart water solubility on the complexes, and their relatively hydrophobic cavities bind a variety of organic guest molecules. A brief overview of the striking structures born of this motif is now given. For a more detailed discussion we refer the reader to a recent review.^[82]

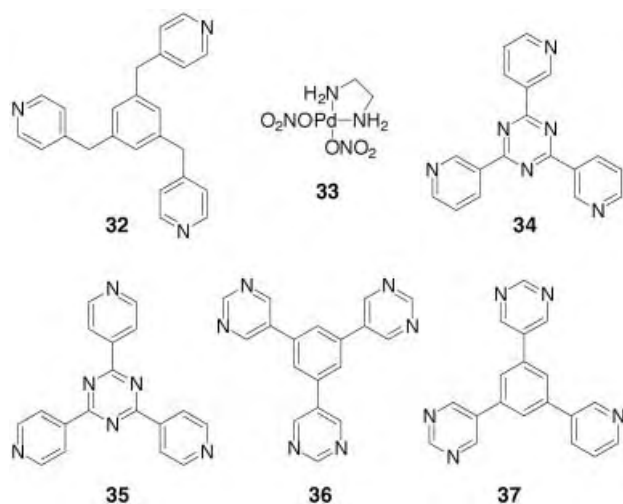


Figure 12. Triangular pyridine/pyrimidine ligands for the construction of supramolecular capsules, and the palladium subunit (**33**) commonly used to stitch them together.

The simplest of these systems is created when a tris(pyridylmethyl) ligand (**32**) is combined with Pd-based corner unit **33** in the presence of a suitable organic guest.^[83] Two ligands of **32** bind a total of three metal centers (Figure 13a) to produce a C_{3v} -symmetric supramolecular capsule (**38**). The palladium–pyridine bonds are stable in protic solvents and the high overall charge (+6) of the complex imparts water solubility. The hydrophobic interior of the capsule is aptly filled by organic anions such as adamantanecarboxylate. The subunits aggregate into an uncharacterized oligomeric state in the absence of a suitable guest.

Analogous rigid planar threefold-symmetric ligands form higher order geometric structures. Ligand **35**, with three 4-pyridyl subunits around a central triazine core, forms supramolecular capsule **41** in the presence of a *cis*-protected square-planar Pd or Pt subunit (Figure 14a).^[84] The metal atoms reside at each corner of an octahedron with the longest metal–metal separation being 1.9 nm and the volume en-

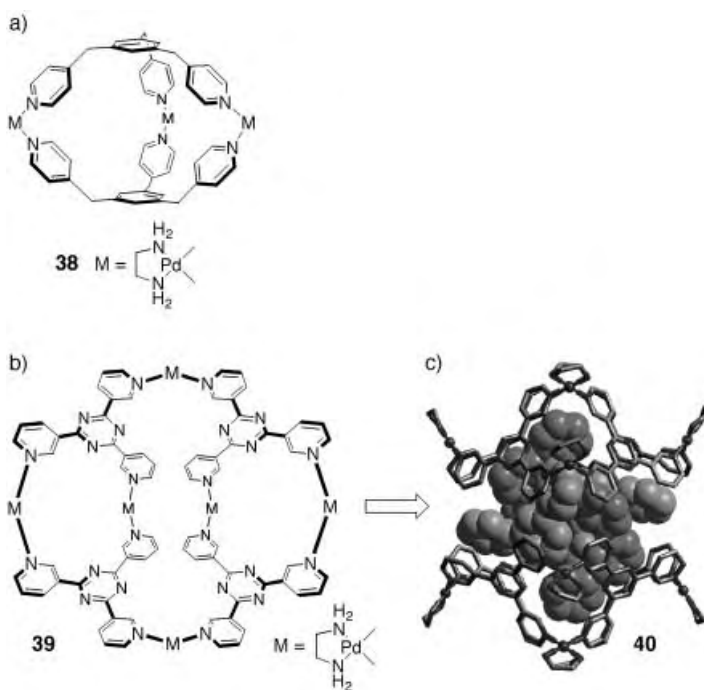


Figure 13. a) A supramolecular capsule built from two flexible ligands and three metal subunits. b, c) Self-assembly of a C_3 -symmetric ligand into a bowl-shaped structure which undergoes a hydrophobic dimerization. Four copies of *m*-terphenyl are encapsulated (shown as CPK models). (Reprinted with permission from ref. [89].)

closed by the capsule about 500 Å³. The platinum-based capsule **41c** is remarkably stable^[85] and encapsulates several guests the size of adamantane.^[86] The encapsulation of four copies of each guest takes place in a cooperative manner that is independent of the nature of the guest. In contrast, tris(pyrimidine) ligand **36** forms a hexahedral supramolecular capsule when combined with a small excess of Pd^{II} complex **33** (Figure 12).^[87] The self-assembly of this hexahedral structure entails recognition and binding among a total of 6 triangular ligands and 18 metal ions. Unlike the previous structure (**41**) in which planar ligands filled alternating faces of a polygon, each face of the hexahedral capsule **42** is completely enclosed by the planar threefold-symmetric ligands (Figure 14b). The volume of the cavity enclosed by this capsule is considerable (about 900 Å³), but only water or small gas molecules may pass through the meager pores (2 × 2 Å) in the structure. Ligand **37**, a variant of **36**, also gives rise to a capsule with hexahedral geometry analogous to that of **42** (Figures 12 and 14), but with some vacant metal binding sites that result in formation of hydrophobic clefts.^[88] These apertures allow for the encapsulation of small molecules such as CBr₄, a behavior that is not displayed by the parent capsule.

The 3-pyridyl-substituted ligand **34** is unable to form a closed-shell topology with organometallic corner subunits. Instead, four copies of ligand **34** and six copies of Pd-subunit **33** self-assemble into an open bowl-shaped structure **39** (Figure 13b).^[89] These hemispherical superstructures assemble in water into discrete dimeric supramolecular capsules (**40**) in the presence of large aromatic guests (Figure 13c). X-ray crystallographic studies reveal that four copies of *m*-terphenyl or six copies of *cis*-stilbene form compact hydro-

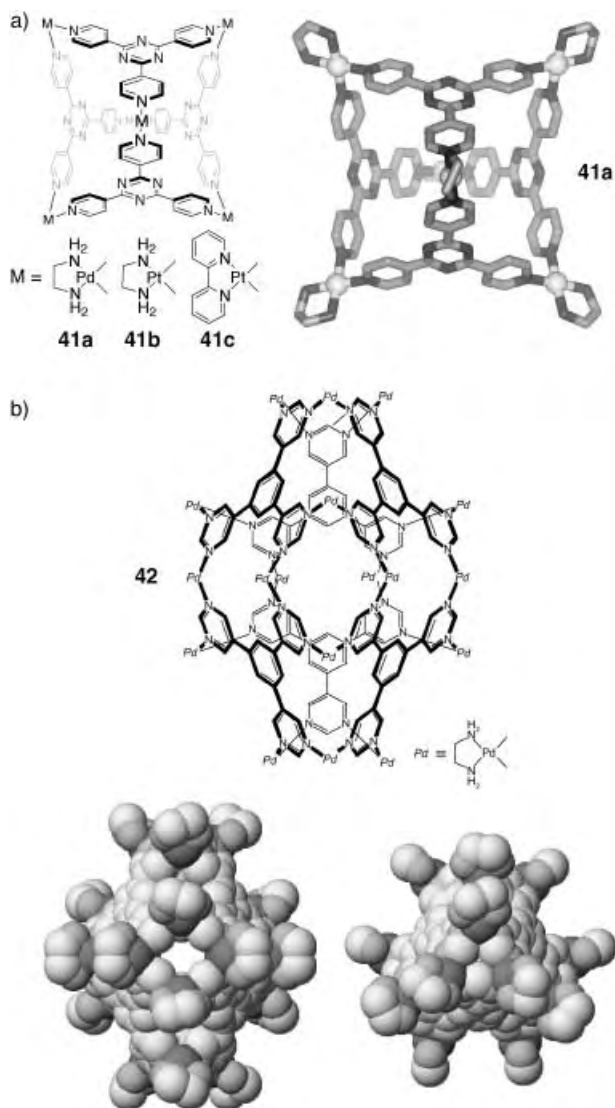


Figure 14. a) A supramolecular capsule constructed from 4 triangular ligands and 6 metal units. The metal atoms define the corners of an octahedron and the ligands occupy alternating faces. b) A hexahedral supramolecular capsule composed of 18 metal ions and 6 triangular ligands. (Reprinted with permission from ref. [87].)

phobic clusters that are encapsulated by the discrete dimeric superstructure. Only dispersive forces and the hydrophobic effect act to hold the capsule together—there is no direct metal–ligand bonding between the supramolecular bowls that comprise the capsule halves. In the absence of direct contacts between the molecules that make up the bowls, it is the guests—bound within both bowls—that provide the bridging interactions that drive dimerization.

The metal-induced self-assembly of non- C_3 -symmetric ligand **43** (Figure 15a) is guest-dependent.^[90] An open cone structure made up of four ligands and eight metals is formed in the presence of benzil. More remarkable is that the addition of CBr_4 drives the assembly of the four triangular ligands and eight metal centers into a closed-shell tetrahedral capsule **44** (Figure 15a). In this case the ligands are arranged in a head-to-tail manner, and fill each face of the tetrahedron so as to completely surround the encapsulated guest.

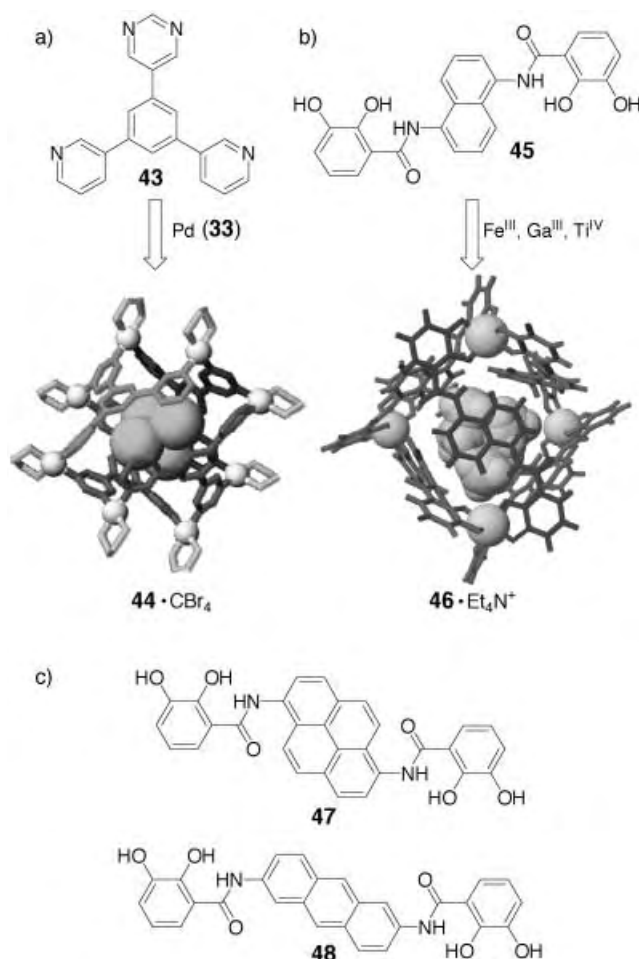


Figure 15. Self-assembly of tetrahedral supramolecular metal–ligand clusters: a) four triangular ligands **43** occupy the faces of the tetrahedron containing eight metal ions (reprinted with permission from ref. [88]), b) four metal ions define the corners of the tetrahedron and six ligands span the edges, c) two other bis(catechol) ligands that form tetrahedral capsules in a manner analogous to ligand **45**.

2.5. Tetrahedral Metal–Ligand Clusters as Supramolecular Capsules

Other motifs have been explored for the creation of tetrahedral ligand–metal clusters. Saalfraank et al. have reported a family of M_4L_6 capsules of tetrahedral symmetry,^[91, 92] and have also shown one example that encapsulates its NH_4^+ counterion.^[93] Other research groups have achieved similar results with different metal–ligand combinations, the encapsulated species being either a counterion or adventitious solvent molecule.^[94–99]

The rich host–guest chemistry of tetrahedral metal–ligand clusters has been beautifully developed by the research group of Raymond. In their system, six bis(catechol) ligands span the edges between four metal atoms that define the corners of a tetrahedron. Most bridged bis(catechols) form M_2L_3 helicates as the thermodynamically most-favored framework, but here the structure of the spacer between the catechol ligands instructs the assembly. Bis(catechol) **45** is linked with a spacer that encourages the adoption of a rigid C_2 -symmetric conformation. The beautiful self-assembly of M_4L_6 tetrahedral

clusters **46** is observed when the ligand is combined with Ti^{IV} , Ga^{III} , or Fe^{III} ions (Figure 15b).^[100, 101] The capsule bears a net -8 charge, and reveals an aptitude for binding positively charged guests. The tetrahedral clusters select tetraalkylammonium guests on the basis of size, yet are also capable of adjusting their cavity volumes from about 200 to 300 Å³ in response to guests of different sizes.^[102] Like **24**, they form complexes-within-complexes through the encapsulation of small alkali ions held by crown ethers.^[103] The pyrene-bridged ligand **47** (Figure 15c) self-assembles into a tetrahedron only in the presence of guests, which are bound in a manner analogous to that with **45**,^[104] while the anthracene-bridged ligand **48** displays more intricate behavior.^[105] In the absence of guests, the combination of **48** with appropriate Ti^{IV} or Ga^{III} subunits results in the formation of the M_2L_3 helicate as the most stable supramolecular structure. The addition of tetramethylammonium ions to the mixture, however, orchestrates a spontaneous rearrangement to the capacious M_4L_6 tetrahedral cluster. Here, the binding of a relatively small guest molecule provides the thermodynamic bias for a wholesale reorganization of six large organic ligands and four metal centers. More complex metal–ligand systems based on multiple copies of two different metals bridged by ditopic ligands have also been developed, but their guest encapsulation properties have not yet been fully explored.^[106]

3. The Ins and Outs of Encapsulation Complexes

3.1. Guest Dynamics and Behavior

Encapsulation places obvious constraints on the translational motion of the guest molecule. Böhmer and co-workers provided some of the earliest understanding of dynamics within the calix[4]arene–tetraurea capsules **14** (Figure 4). The diffusion coefficients of encapsulated and free guest molecules were determined by the pulse gradient spin echo (PGSE) NMR technique.^[107] The diffusion coefficients of the encapsulated guests were found to match well with those of the assembled host, while those of the free guest were much higher.

The effects of encapsulation on the guest's rotational freedom is usually apparent from the NMR spectra. Benzene tumbles rapidly and *p*-xylene slowly on the NMR timescale in the cylindrical capsule **18** (Figure 6); toluene shows a broadened signal characteristic of an intermediate tumbling rate. In the softball **3b** (Figure 1) with encapsulated [2.2]paracyclophane, ¹³C spin-lattice relaxation studies gave evidence of correlated bulk host–guest movement. This large guest is apparently wedged into a limited space.^[108]

The research group of Böhmer took advantage of hydrogen-bonded calixarene capsules (**14**) with decreased symmetry to study the rate of capsule dissociation (0.26 s^{-1}) and the rate of guest exchange (0.47 s^{-1}) using ¹H NMR NOESY experiments.^[109, 110] The intimate relationship between the host and guest is also reflected in the determination of the geometry and dynamics of an encapsulated guest through NMR spectroscopic analysis of the host alone. The overall symmetry of the host complex is affected by the binding

orientation and dynamics of the guest molecule bound within the cavity. In one elegant example by Fujita and co-workers, simple 1D NMR studies on host **41** (Figure 14) yielded detailed information on both the binding orientation and the temperature-dependent dynamics of the included guest.^[111]

Effects on the guest's internal molecular dynamics are also directly measurable. The ring inversion of cyclohexane within capsule **6** (Figure 2) was studied through the use of [D]₁₁-cyclohexane as a guest molecule.^[112] The barrier to ring inversion within the flattened cavity of **6** ($10.55 \text{ kcal mol}^{-1}$) is increased by $0.3 \text{ kcal mol}^{-1}$ relative to the value found in free solution ($10.25 \text{ kcal mol}^{-1}$); ground-state stabilization through CH- π interactions within the cavity is thought to be the cause for this difference. The encapsulation of [D]₁₁-cyclohexane within a calixarene–tetraurea capsule (**14**, Figure 4) that described a roughly spherical cavity resulted in no observable change in the barrier to ring inversion. Conversely, the internal dynamics of 1,4-dioxane and 1,4-thioxane encapsulated within capsule **19** (Figure 6) are significantly restricted.^[113] Despite the pseudo-spherical nature of the cavity surrounding the guests, the barrier to conformer interconversion is increased by a relatively large 1.6 – $1.8 \text{ kcal mol}^{-1}$ upon binding. In general, these experiments suggest that the internal dynamics of included guests are controlled specifically by host–guest interactions.

3.2. Control of Guest Release

For the development of encapsulation-based applications it is more urgent to control guest exchange than to understand it. The guests within most hydrogen-bonded capsules are liberated by the addition of solvents that compete effectively for hydrogen bonds. The dissociation is thermodynamically and kinetically facilitated by these competitive solvents. Capsules based on metal–ligand interactions are in general subject to decomposition (and concomitant guest release) by the addition of strong nucleophiles and/or subjection to elevated temperatures. Although these environmental changes do successfully bring about the liberation of guests, there is a need for more specific and reversible methods for the control of guest encapsulation and release.

A convenient stimulus for the reversible control of many metal–ligand based encapsulators involves changes in pH values. Harrison and co-workers have used pH changes to reversibly trigger the self-assembly of resorcinarene–iminodiacetate capsules and accompanying guest encapsulation.^[77] The cobalt-based capsule **29** (Figure 10) is assembled at pH 6, but exists in a monomeric state at pH 1. The exchange between these two states is reversible. The uptake of gases in the tennis ball **2c** (Figure 1) has also been controlled by the action of acids and bases on the peripheral amino groups.^[39]

Instead of altering the structural components of the capsule, guest release can be accomplished most simply by guest exchange. If the system is under thermodynamic control (as are most self-assembled capsules) then the weakly held guest is displaced by the strongly held one. One example of this type of supramolecular substitution reaction is the exchange of adamantane with paracyclophane in the softball **3b** (Fig-

ure 16).^[114] At the millimolar concentrations convenient for study by NMR spectroscopy the exchange takes place with a half-life of about one hour and the process has much in common with conventional substitution reactions. At low concentrations of the incoming guest the slow step is S_N2 -like, while at high concentrations of the incoming guest the slow step is S_N1 -like. In both cases, complete dissociation of the capsule is not necessary, as this would rupture all 16 hydrogen bonds. Instead, a lower energy process is proposed that involves opening “flaps” on the softball’s surface (Figure 16). This exposes the resident guest to the incoming “nucleophile,” which is either the solvent or new guest. As a consequence the guest exchange is faster than dissociation (see Section 4.1).

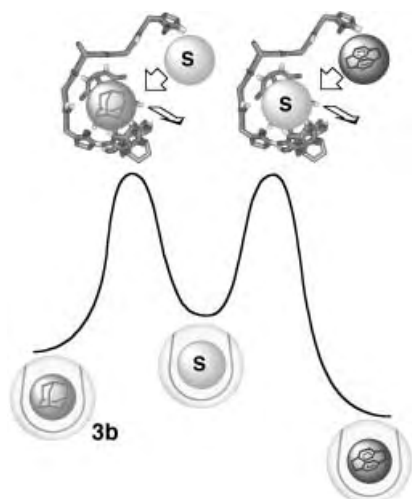


Figure 16. A two-step substitution reaction in a supramolecular capsule. The solvent-filled capsule is intermediate in the replacement of adamantane by the thermodynamically more favored [2.2]paracyclophane. Partially open capsules are proposed as transition states (S = solvent).

4. Form to Function

Supramolecular chemistry has matured to a degree that the design and synthesis of molecules that self-assemble into predictable supramolecular structures is becoming routine. Much of this research is curiosity driven, but the application of self-assembling systems to the development of functional devices should not be ignored, particularly in this, the “nano” decade. The development of functional properties from self-assembly is merely the first step towards this goal.

4.1. Chirality in Encapsulation Complexes

Chiral supramolecular complexes are always popular topics, especially when noncovalent interactions direct the assembly of achiral components into chiral superstructures. In the absence of a chiral bias the structures appear as racemates, but with chiral information present in the system, the spontaneous formation of an excess of the appropriate supramolecular structure can be the outcome.^[115, 116] Several studies have taken advantage of the intimate relationship between encapsulated molecules and the supramolecular

capsules that bridle them, thus granting a unique perspective on the transfer of information within complexes that is governed by noncovalent interactions. At the outset, the larger distances (compared to covalent bonds) and the flexibility of the weak, often nondirectional forces, did not guarantee success.

The tendency for calixarene–tetraurea monomer **13b** functionalized with aryl sulfonamides to exclusively (>98%) form heteromeric capsules with monomer **13a**, functionalized with a simple aryl group, has previously been discussed in Section 2.2.^[52] When heteromeric dimers such as **13a**·**13b** form, the cyclic directionality of the urea hydrogen bonding seam results in the generation of racemic chiral species (Figure 17b).^[54] The head-to-tail arrangement of the

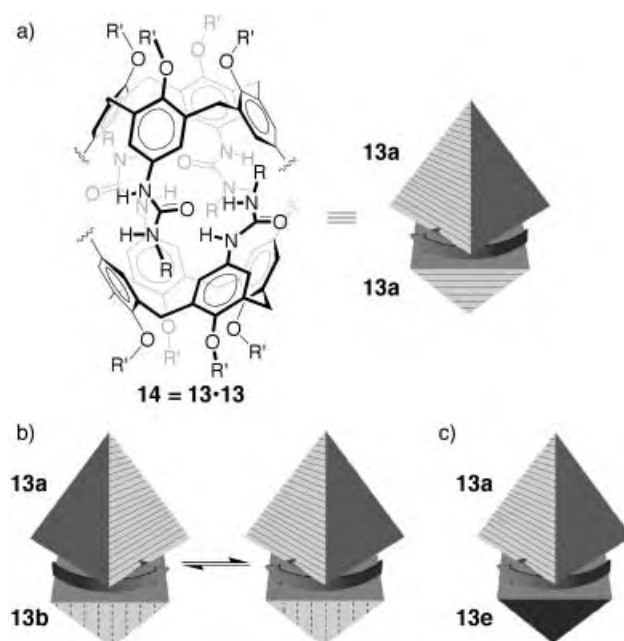


Figure 17. Chirality in calix[4]arene–tetraurea capsules: a) cyclic directionality of the urea hydrogen-bonding seam, b) capsules constructed from two different achiral components (for example, **13a**·**13b**) are formed as equilibrating cycloenantiomers, c) the presence of chiral groups on one of the two subunits can induce complete selectivity in urea directionality to produce an optically pure capsule (for example, **13a**·**13e**).

urea units at the equator can be clockwise or counterclockwise, given a reference point of the poles. Interconversion of these enantiomers occurs through the rotation of functional groups that make up the hydrogen-bonding seam, or through complete dissociation and recombination of monomers. Either mechanism would require the eventual breaking of all 16 hydrogen bonds, and as such the reversal of hydrogen-bonding directionality (and thus interconversion of enantiomers) is slow on the NMR timescale.^[109] Chiral guests, however, were not capable of significant differentiation of the two resulting enantiomeric capsules **13a**·**13b**.^[54]

A bias was introduced with chiral auxiliaries attached to the distal urea nitrogen atom. A screening of amino acid derivatives led to the observation that calixarenes appended in this manner with β -branched amino acids have a predi-

lection for association with calixarenes bearing aryl-substituted urea groups.^[55] Mixing the valine-derived monomer **13e** and aryl monomer **13a** favors the assembly of the heterodimeric capsule **13a·13e** almost exclusively (>98%). This capsule is analogous to the capsule **13a·13b** formed from achiral components. Here, the presence of chiral groups on one subunit results in complete asymmetric induction of the capsule's cycloenantiomerism (Figure 17c). The resulting enantio- and diastereopure capsule **13a·13e** shows an approximately 13% excess of one diastereomeric complex for the binding of the chiral guest norcamphor from a racemic mixture. The chiral auxiliary groups are not in direct contact with the encapsulated guest molecule. Instead, their influence is transmitted to the guest through the directionality imparted to the hydrogen-bonding seam that lines the cavity.

Glycoluril-based monomers (Figure 1) have also been employed in the construction of chiral self-assembled capsules. The simple monomers (**1**, **3**) contain two mirror planes, which are both preserved in the dimeric assembled state. Analogous monomers lacking one of the two mirror elements have been synthesized.^[117] These monomers are achiral, but self-assemble into dimeric supramolecular capsules that retain no mirror planes in the assembled state (Figure 18a).

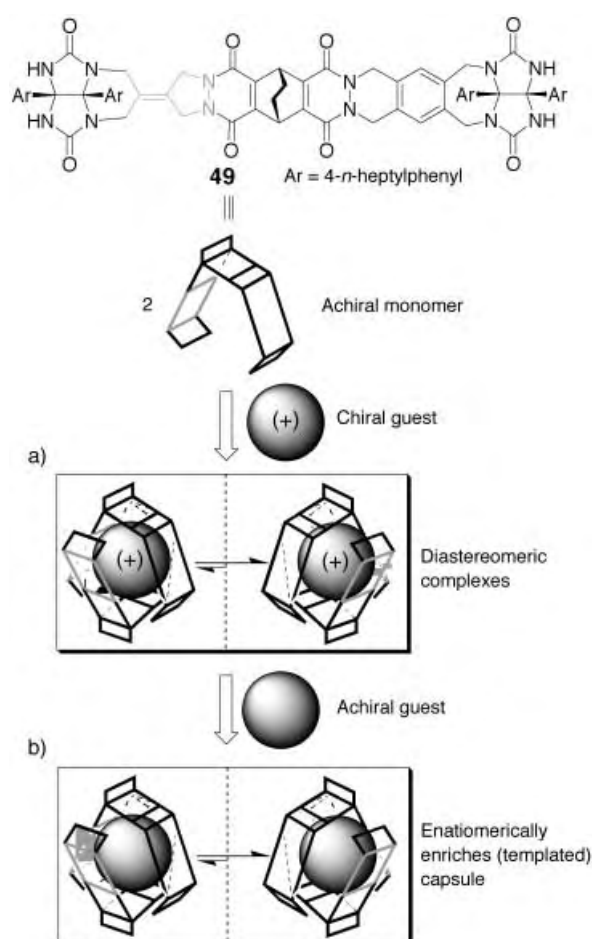


Figure 18. “Softball” monomers possessing only one mirror element spawn dimeric structures lacking any mirror symmetry: a) the host is templated with a chiral excess by the binding of a chiral guest, b) host racemization is slow following removal of the chiral guest and the enantiomeric excess of the capsule persists for several hours.

Again, the chiral capsules formed from these achiral components are formed as an equilibrating racemic mixture. The use of monomer **49**, which incorporates symmetry-breaking elements adjacent to the encapsulated guest, results in a host–guest pair capable of significant transfer of chiral information.^[118, 119] The binding of an enantiomerically pure guest can bias the self-assembly process (a form of imprinting) such that one enantiomeric capsule is favored over the other by as much as a factor of four. In a reversal of the flow of chiral information, this diastereomeric host–guest complex can then be used for noncovalent chiral templating (Figure 18).^[120] In this procedure, an optically pure guest is used to imprint the formation of a single chiral softball enantiomer and is then rinsed out rapidly by an excess of an achiral guest or solvent molecule. Since the exchange of guests in glycoluril-based capsules is much faster than the dissociation of the capsule, the exchange occurs without racemization of the capsule itself. The ghost of the chiral guest allows the chiral capsule to discriminate between guest enantiomers for several hours before it returns to its thermodynamically determined state.

A recent study by Shinkai and co-workers has revealed a capsule that possesses helical chirality.^[121] Monomer **50** (Figure 19) undergoes metal-directed self-assembly to form a dimeric capsule analogous in structure to **27** (Figure 9). The decreased angle of the ligating atoms in **50** (120°) relative to **27** (180°) results in a *trans*-substituted metal subunit being utilized for the formation of a closed-shell dimeric assembly (**51**). The binding of alkali metal ions at the oxygen-rich lower rim of homooxocalix[3]arenes is known to affect the geometry and binding properties of the capsules constructed from such building blocks.^[76] In the case of **51**, the binding of Na^+ ions

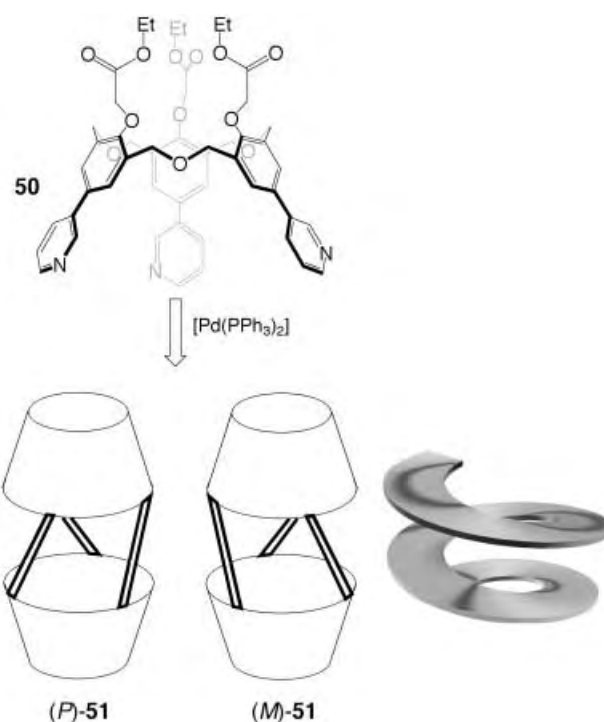


Figure 19. A homooxocalix[3]arene monomer forms helically chiral dimeric capsules in the presence of suitable metal subunits.

induces a dramatic conformational shift that yields a helical arrangement of the capsule walls down the long axis of the capsule (Figure 19). Both *M* and *P* enantiomers are formed, as revealed by experiments with chiral shift reagents. As in the softball, chiral guests are able to induce a bias (up to 55% for the encapsulated (*S*)-2-methylbutylammonium ion) in favor of one helical enantiomer over another.

In another example, the direction of chiral information flow is reversed. Derivatization of compound **9** (Figure 3) with a single hydroxy group provides a new monomer (**52**) that is chiral and resolvable into single enantiomers (Figure 20).^[122] Self-assembly occurs spontaneously in the presence of an appropriate guest, and the enantiopure capsule (**53**) exhibits enantioselective (d.e. 60%) binding of chiral guests from a racemic mixture. The interaction of a single copy of monomer **52** with a single chiral guest molecule is presumed to offer a small energetic differentiation, but significant chiral recognition emerges when multiple copies of monomer **52** form a closed chiral space.

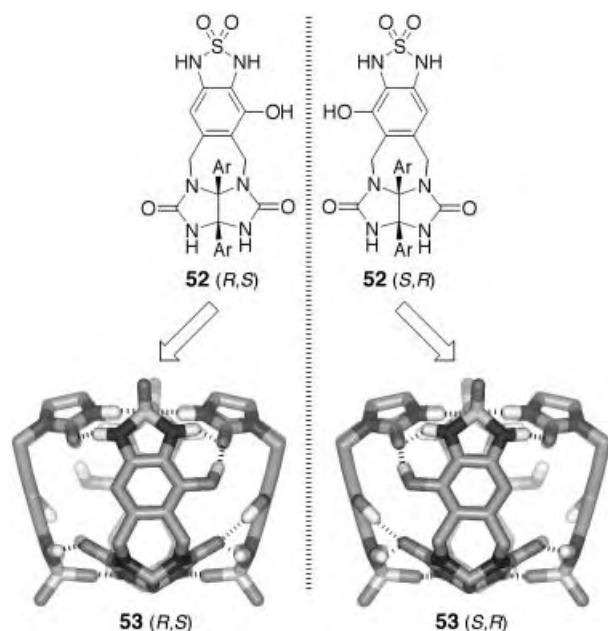


Figure 20. The self-assembly of an enantiopure monomer yields a chiral tetrameric capsule capable of discriminating between guests on the basis of chirality.

A common origin of chirality in metal-based supramolecular complexes is the Δ/Λ helical chirality associated with the octahedral arrangement of three bidentate ligands around a metal center. The tetrahedral clusters of Raymond and co-workers^[101] demonstrate the spontaneous generation of supramolecular chirality within self-assembled capsules based on metal ligation. The chirality of the four metal centers present in each tetrahedral cluster is strongly coupled by the bis(catechol) ligand **45** (Figure 15); the $\Delta\Delta\Delta\Delta$ and $\Lambda\Lambda\Lambda\Lambda$ clusters are formed to the exclusion of clusters of mixed configurations. The two resulting diastereomeric complexes formed when the (–)-*N*-methylnicotinium cation is encapsulated by Ga^{III} complex **46** (Figure 21) can be easily separated.^[123] Removal of the chiral guest by replacement with the

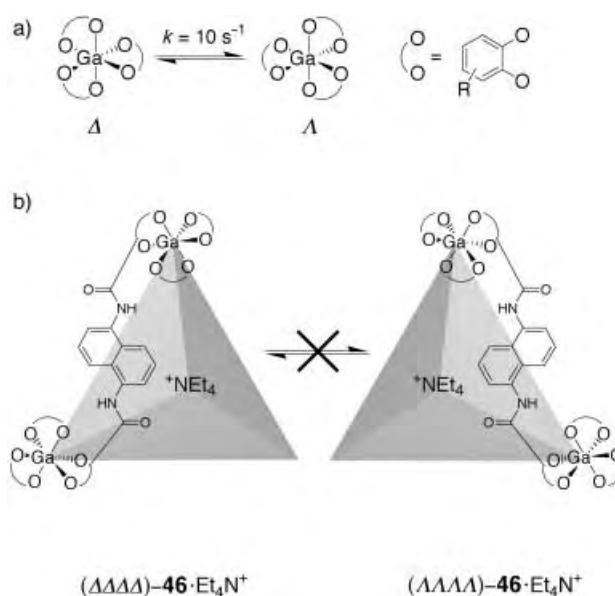


Figure 21. a) Facile racemization between the Δ and Λ configuration of chiral octahedral gallium(III) catecholates. b) An optically pure self-assembled tetrahedron containing four such metal centers in a mechanically linked framework is isolated through encapsulation of a chiral guest, and is stable to racemization even after extended heating.

achiral Et_4N^+ ion yields the enantiopure tetrahedral clusters $\mathbf{46} \cdot \text{Et}_4\text{N}^+$. The mechanical coupling of metal centers within the tetrahedral framework not only favors the presence of four homoconfigurational metal centers in a cluster, but also confers to each metal center a remarkable resistance to racemization. The racemization rate for isolated tris(catecholate)– Ga^{III} centers is fast (10 s^{-1}) at room temperature. In contrast, an aqueous solution of $(\Delta\Delta\Delta\Delta)\text{-46} \cdot \text{Et}_4\text{N}^+$ remains enantiopure after eight months at room temperature, and even extended heating does not induce racemization.

4.2. Dynamic Libraries of Molecular Receptors

Great diversity can be generated through the combination of relatively few components and a large library of multicomponent species can be developed. Lehn has pioneered the field of dynamic combinatorial chemistry, in which the composition of equilibrating libraries of molecular receptors is trained by the presence of the desired target.^[124–127] Molecular capsules are suitable candidates for this treatment. As such, the selection of molecular receptors from a library under thermodynamic control has been achieved by both hydrogen-bonded and metal–ligand based supramolecular capsules.

Our efforts involved the monomer **9** that self-assembles to form hydrogen-bonded tetrameric capsule **10** (Figure 3). The variation of the substitution patterns at the central aromatic carbon atom gave a total of five complementary (and self-complementary) subunits (**9**, **52**, **54–56**, Figure 22). The added functionality doesn't disrupt the forces responsible for the assembly but does modify the size, shape, and chemical lining of the cavity. The five monomers represent a library of 613 possible tetrameric capsules with 70 different compositions.^[128] The mixture was monitored by using electrospray

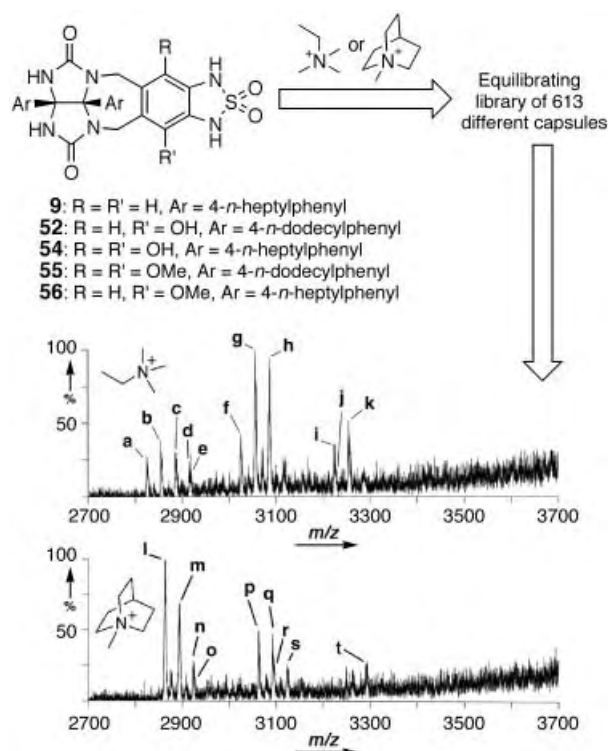


Figure 22. A dynamic library of self-assembled tetramers arises from the combination of five complementary monomers. Each letter indicates a mass spectral peak corresponding to a unique molecular host that forms in varying quantities in response to the presence of different guest molecules. The composition of the library is biased towards the hosts that interact most favorably with the added guest.

mass spectrometry, a method that has recently come of age in the characterization of supramolecular complexes.^[129, 130] The distribution of tetrameric capsules was measured by taking advantage of mass-labeled monomers. The composition of the mixture depends strongly on the nature of the guest: the receptors that best fit the structure of the added guest molecule spontaneously emerge as the predominant species in solution.

In another example, a variant on the tris(pyridine) triangular ligands (Figure 12) developed by Fujita and co-workers, is the set of supramolecular capsules arising from mixing one 4-pyridyl and two 4-pyridylmethyl subunits as ligands with a single metal unit as an adhesive. The C_3 symmetry of the ligand (**57**) is broken, and metal-mediated self-assembly gives two isomeric capsules (Figure 23). The formation of the two receptors is strongly guest-dependent: one is favored by aromatic guests, while the other is favored by more spherical guests such as CBr_4 .^[131] The diversity of receptors present in the library was increased by the addition of another ligand, **32**. Equilibration within the resulting library of four receptors was efficiently controlled by the presence of suitable guest species (Figure 23).^[132]

4.3. Capsules as Sensors

One function of supramolecular capsules is in small-molecule sensing, and we use an example of calixarenes to show how a binding event gives a detectable signal: a common transduction path is used for the detection of analytes at low concentration. Calixarene-tetraureas **58** and **59** were substituted^[52] at the lower rim with fluorescent dyes (Figure 24).^[133] The self-assembly and encapsulation processes of these monomers proceed in the usual manner with heteromeric capsule **60** preferred to the formation of each homodimer (as in **13a**–**13b**). The dyes were selected such that the emission spectrum of one dye (the donor, **58**) overlaps the excitation spectrum of the other (the acceptor, **59**). When the two dyes are in proximity to one another, excitation of the donor results in significant fluorescence resonance energy transfer (FRET) to the acceptor, and emission at the acceptor's emission wavelengths is observed. The result is a FRET signal that is dependent on the assembly of **58** and **59**. Nonspecific aggregation is negligible at the nanomolar concentrations of the experiment, and no FRET is observed in the absence of a suitable guest species. In the presence of a

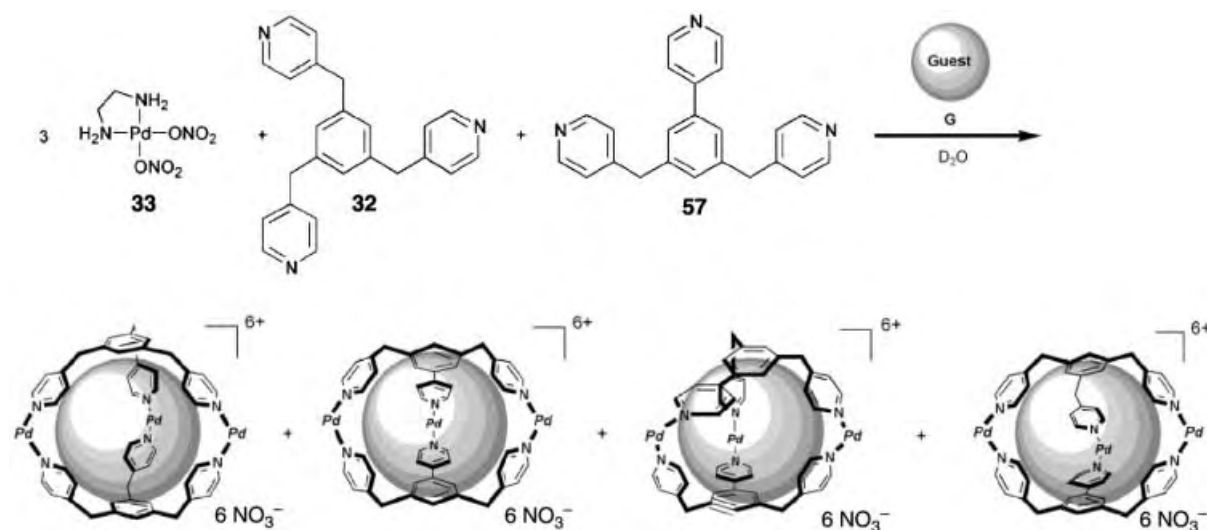


Figure 23. A dynamic library of four receptors arising from the combination of two ligands in the presence of a suitable metal subunit. Spherical guests such as CBr_4 or CBrCl_3 give rise to different hosts than include aromatic guests such as benzene or *p*-xylene. (Reprinted with permission from ref. [132].)

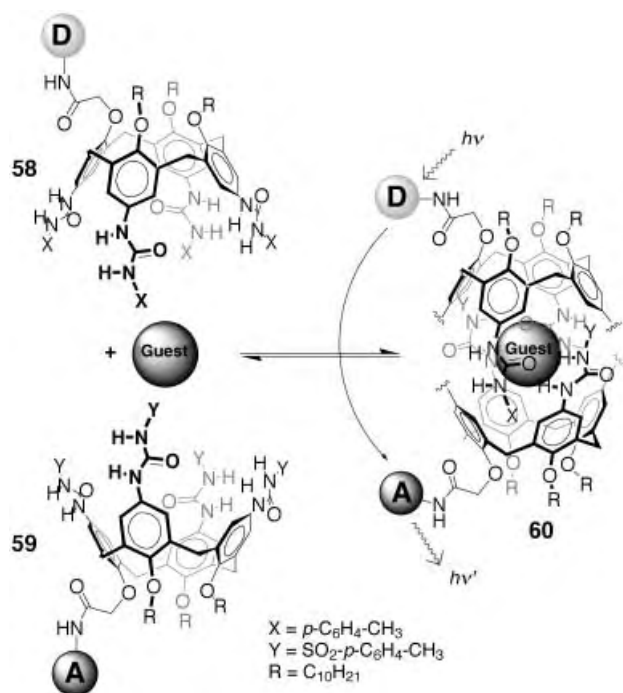


Figure 24. Encapsulation-dependent sensing of a guest. The presence of a guest encourages capsule dimerization, which in turn produces an optical signal through fluorescence resonance energy transfer between dyes covalently attached to each monomer.

suitable guest, encapsulation occurs and a FRET signal arises. In this way the encapsulation-dependent detection of 3-methylcyclopentanone was achieved by the combination of **58** and **59** in *p*-xylene.

4.4. Self-Assembled Capsular Polymers

New structural and physical properties emerge from the polymeric assembly of compound **61**, produced by covalently coupling a calixarene–tetraurea monomer at the lower rim to another calixarene–tetraurea monomer (Figure 25a).^[52, 134] The use of a rigid linker creates divergent tetraurea recognition elements that are unable to bond in an intramolecular sense. Instead, the encapsulation-driven self-assembly results in a polymeric chain of capsules (Figure 25b). Like other polymers, “polycaps” display new properties on the macroscopic scale. Unlike traditional polymers, the chains use reversible interactions and are formed under equilibrium conditions. Polarized light microscopy studies on concentrated solutions of **61** reveal that the polymer displays a nematic liquid crystalline state, that is, the polymer chains self-organize in a linear array.^[135] Chiral nematic (cholesteric) liquid crystalline phases emerge from analogous chiral monomers. Fibers that are pulled from the liquid crystalline melt also display order under a polarized light microscope, a behavior that is, perhaps, responsible for their surprising strength (crude measurements show that these fibers have a yield stress within an order of magnitude of that of covalent polymer fibers such as nylon-6). These samples also display bulk viscoelastic properties related to their polymeric nature.^[136]

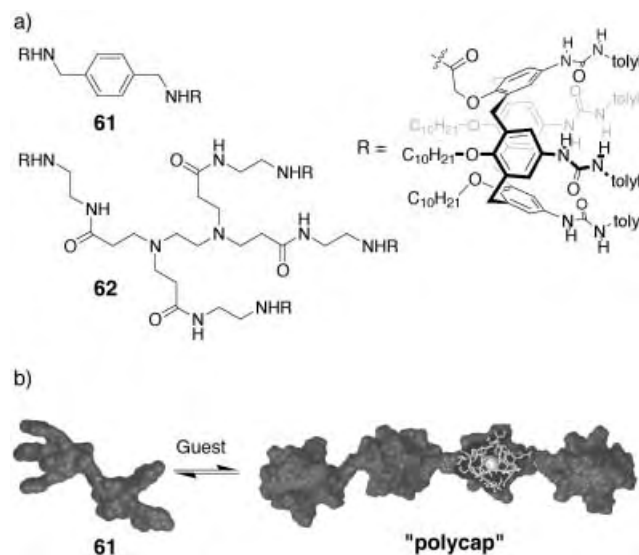


Figure 25. Encapsulation-dependent polymerization and gel formation. Monomer **61** forms polymeric chains of capsules (polycaps) in the presence of a suitable guest. Addition of noncovalent cross-linker **61** results in the formation of physical gels.

The doping of monomer **61** with a compatible cross-linking species (**62**) has dramatic effects on the bulk properties of the mixture.^[136] Compound **62** relies on encapsulation to form self-assembled cross-links between polymer chains. Cross-linker **62**, when present in concentrations as low as 5% relative to **61**, causes the formation of a gel phase. These gels are reminiscent of conventional physical gels, in which covalent linear polymers are cross-linked by weak noncovalent interactions. Here, the structural components are reversed, but the viscoelastic behavior of the gels is quite similar. For example, the gels are dilatant: their viscosity increases with the application of shear. This result points to increased ordering under anisotropic flow, and ordered structures have been observed in surface transmission electron microscopy images obtained from frozen chloroform.

In every case, the bulk properties of the polycaps are dependent on the presence of a suitable guest species and a solvent that does not compete for hydrogen bonds. The formation of polymeric chains, liquid crystalline phases, viscous polymeric solutions, and gels are properties fundamentally derived from, and dependent on, molecular encapsulation.

5. Control of Reactivity through Encapsulation

The most direct illustration of the effects of encapsulation on small molecules is the mediation of chemical reactions. Encapsulated molecules are removed from a sphere of solvation and placed in enforced proximity to the host and, if space permits, to other guests. This constrained environment governs the guest’s encounters with potential reactive partners, as well as fundamentally altering the concentration (molecules per volume) of reactive species. This influence is exerted for the duration of the lifetime of the encapsulation complex, which may be from microseconds to hours.

5.1. Acceleration and Catalysis

Two different approaches to supramolecular catalysis through encapsulation have been reported in the literature: 1) bimolecular catalysis can occur when two reactive partners are bound within a single capsule and 2) phase-transfer catalysis can occur when the capsule transports guests from one solvent phase to another. Both rely on turnover, the release of product (or passenger) and the re-uptake of reactants. Reversibility is the key to this behavior.

Initial reports of the self-assembled softball (**3**, Figure 1)^[40] and its propensity for the simultaneous encapsulation of two guest molecules^[41] raised the possibility of catalyzing a bimolecular reaction by encapsulation. Rate acceleration through encapsulation was observed in the Diels–Alder reaction of benzoquinone (**63**) and cyclohexadiene (**64**) mediated by **3b** (Figure 26a).^[137] In the resting state of the system two molecules of benzoquinone are encapsulated

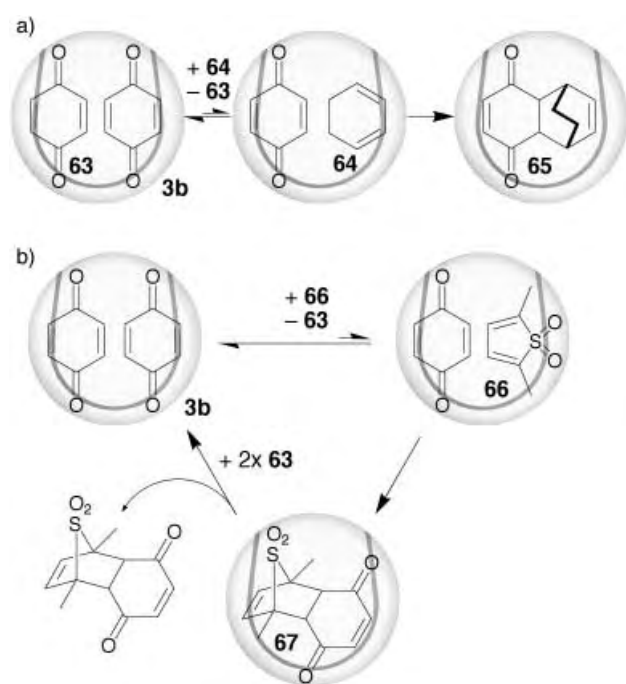


Figure 26. Diels–Alder reactions mediated by a self-assembled capsule: a) the reaction of benzoquinone and cyclohexadiene is accelerated through encapsulation, but product inhibition prevents catalytic turnover, b) the reaction of benzoquinone and **66** is accelerated by the capsule, and subsequent dissociation of product results in catalytic turnover.

strongly by **3b**: neither the capsule containing only cyclohexadiene nor the mixed encapsulation complex can be observed by NMR spectroscopy. Nevertheless, an encapsulation-dependent rate acceleration of nearly 200-fold occurs in the Diels–Alder reaction between the two substrates. The rate acceleration likely arises from a mixed encapsulation complex, the counterpart of the Michaelis complex.^[138] Derivatives of **63** and **64** that are not of appropriate size for encapsulation show no rate acceleration. Addition of a nonreacting guest that competes effectively for the catalytic site (an inhibitor) also prevented rate acceleration. Unfortunately, the product (**65**) of the reaction of **63** and **64** is a good

guest for the capsule, and strong product inhibition prevents turnover, that is, catalysis (Figure 26a). The reaction of **66** with **63** was examined in the expectation that the loss of SO₂ from the Diels–Alder adduct would result in product (**67**) release and catalyst turnover (Figure 26b). Instead, it was found that loss of SO₂ does not occur under the reaction conditions. Nevertheless, the product (**67**) is fortuitously ejected from the softball by the quinone and catalytic turnover is the outcome.^[139]

A different approach to encapsulation-dependent catalysis uses capsules constructed through metal–ligand interactions operating in aqueous environments. Capsule **41a** is highly charged (+12), yet shows a propensity for encapsulating a variety of neutral hydrophobic molecules. This combination of properties make **41a** a unique candidate for the encapsulation-dependent phase-transfer catalysis of reactions in water. The effect of **41a** on the Wacker oxidation of styrene catalyzed by [Pd(NO₃)₂(en)] (en = ethylenediamine) was examined to test this hypothesis (Figure 27).^[140] In the absence of capsule **41a**, the transformation of styrene to acetophenone catalyzed by [Pd(NO₃)₂(en)] proceeds only to a small extent in water (4%) as a result of the substrate's low solubility in aqueous media. Under the same conditions, the

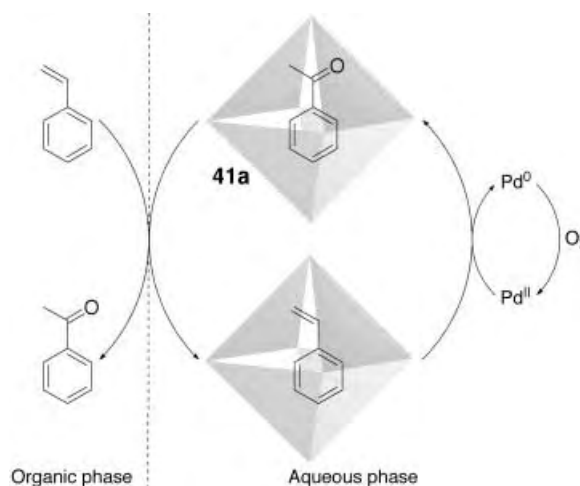


Figure 27. Reverse phase-transfer catalysis of the Wacker oxidation of styrene by a supramolecular capsule.

presence of a catalytic amount of **41a** results in a dramatic increase in the yield of acetophenone (82%). Experiments carried out in the presence of styrene and a competing guest (1,3,5-trimethoxybenzene) decreased product formation dramatically (3%). The structural Pd^{II} components of capsule **41a** alone are not sufficient for catalysis of the reaction; in all cases the addition of catalytic [Pd(NO₃)₂(en)] is necessary. The result is a unique “double catalyst” system wherein **41a** acts as a phase-transfer catalyst and a separate Pd^{II} species acts as the oxidation catalyst (with reoxidation by air). This reverse phase-transfer methodology can be extended to other substituted styrenes that are encapsulated by **41a**.

In another example, complex kinetic behavior reminiscent of autocatalysis is observed when reagents are compartmentalized within a supramolecular capsule.^[141] Dicyclohexylcar-

bodiimide (DCC) is encapsulated by cylindrical capsule **18** (Figure 28). Addition of benzoic acid **68** and aniline **69** to the mixture gives rise to complex kinetic behavior. Trace amounts of DCC free in solution promotes the formation of an amide bond between the acid and amine reactants. The products of this reaction are anilide **70** and dicyclohexylurea (DCU), both of which are better guests for capsule **18** than DCC. Accordingly, increasing amounts of DCC are displaced from the capsule by **70** and DCU, and the rate of the reaction increases as the reaction proceeds. The kinetics possess a sigmoidal character that depends on product formation, yet this is not classical autocatalysis, as there is no single catalyst in the system. The nonlinear kinetics can be viewed as an emergent property of the system as a whole, with the partnership of compartmentalization and molecular recognition giving rise to chemical amplification. This result, while not easily classified, highlights the role that compartmentalization may play in the creation and maintenance of complex systems.

5.2. Stabilization of Reactive Species

Reversibly formed capsules have successfully stabilized species that are not otherwise stable in free solution. The processes that are responsible for self-assembly and encapsulation can provide enough free energy for an encapsulated guest to alter its own internal equilibria. In the simplest of these cases, encapsulated guests display altered conformational preferences. Supramolecular capsules can also stabilize encounter complexes formed between multiple guests that are not otherwise observed. In the most dramatic examples, encapsulation can be used for the stabilization and isolation of reactive intermediates.^[142]

As described in Section 2.2, self-assembled capsule **18** is capable of encapsulating long cylindrical molecules that are complementary in both shape and size to the dimensions of its elongated cavity.^[66] A preference for the binding of *trans*-stilbene over *cis*-stilbene underscores this selectivity.^[143] The binding of *N*-methylbenzanilide (**71**) demonstrates a more subtle set of characteristics imparted by the host capsule. Although **71** is known to prefer the *E* conformation in free

solution, the physical constraints provided by capsule **18** force **71** to adopt the unfavored *Z* conformation (Figure 29).^[143] Like all properties governed by encapsulation, the preferences imparted upon **71** arise from a combination of equilibrium processes. The self-assembly of the capsule, the encapsulation of the guest, and the conformational state of the guest molecule are all dynamic processes that conspire to yield the end result—in this case a simple conformational shift.

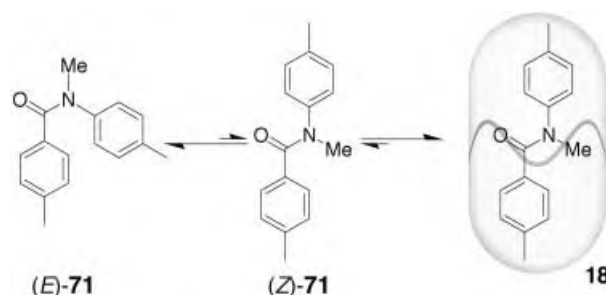


Figure 29. A shift in conformational equilibrium (*E*)-**71** ⇌ (*Z*)-**71** brought about by shape-selective encapsulation within an elongated capsule.

Kusukawa and Fujita used capsules constructed with metal–ligand interactions for the stabilization of unfavored conformations. The treatment of an aqueous solution of capsule **41a** with a solution of 4,4'-dimethylazobenzene (**72**, *cis:trans* 1:6) in hexane results in the formation of an unusual complex within the capsule walls (Figure 30a). The capsule selectively binds two equivalents of *cis*-**72**.^[144] 2D NMR studies using the analogous *cis*-stilbene **73** shows NOE contacts between the vinyl protons and methyl protons of the guest, which provides additional evidence for the proposed dimeric guest cluster. The *cis*-azobenzene molecules are considerably stabilized within this encapsulation complex: exposing the solution to visible light for several weeks did not result in the production of any of the thermodynamically favored *trans*-azobenzene. Molecular modeling studies reveal that the dimeric hydrophobic guest complex is too large to have formed outside the capsule and entered as a single species. Since the structural elements of the capsule are not equilibrating under the conditions of these experiments, the hydrophobic dimer must form within the capsule walls.

This “ship-in-a-bottle” encapsulation process is not unique to azobenzene and stilbene guests. The exposure of Pt-based cage **41c** to phenyltrimethoxysilane results in the formation of a cyclic silanol trimer **74a** within the cavity of the supramolecular capsule (Figure 30b).^[145] Cyclic trisilanol oligomers of this type are considered to be intermediates in the sol–gel condensation. Although the cyclic tetramer has been prepared by other methods, the highly reactive cy-

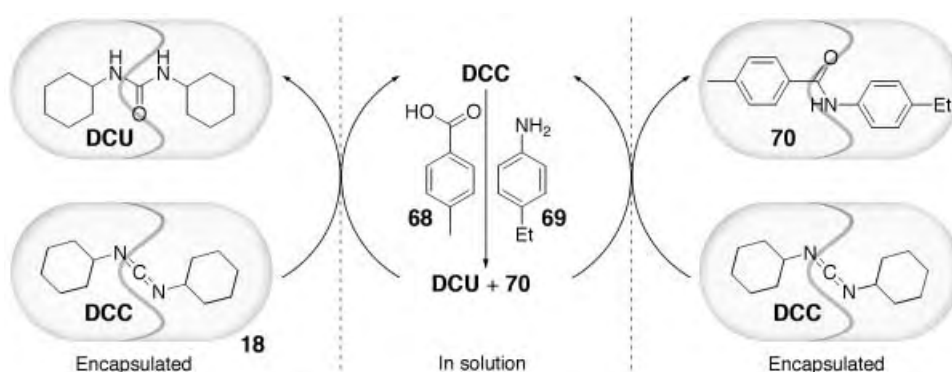


Figure 28. Compartmentalization of reactants and products gives rise to emergent nonlinear behavior. DCC is initially sequestered from the reaction medium through encapsulation within cylindrical capsule **18**. As the reaction between acid **68** and amine **69** proceeds, the coupled product **70** and DCU are generated and both displace DCC from the reversibly self-assembled capsule.

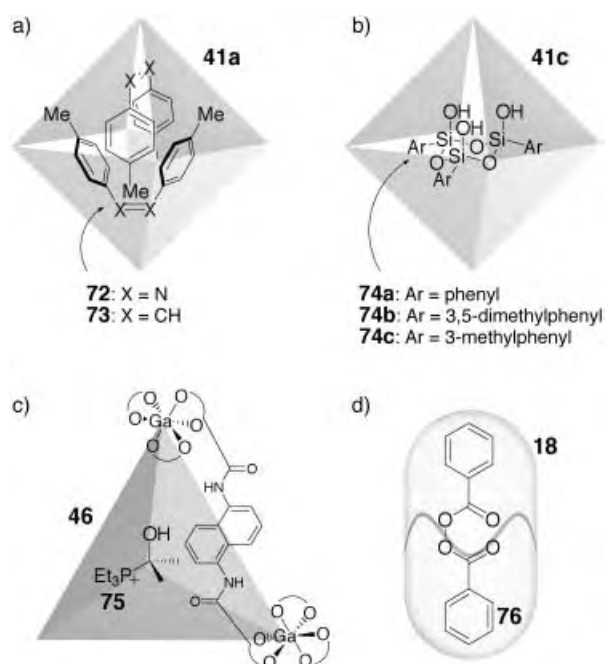


Figure 30. Stabilization of reactive species through encapsulation: a) formation of unique tennis ball shaped hydrophobic dimers **72** and **73** within a metal-based supramolecular capsule **41a**; b) encapsulation and stabilization of highly reactive cyclic trisilanol **74a–c**, proposed to be intermediates in the sol–gel polycondensation process; c) formation of a water-sensitive phosphane–acetone adduct **75** within a tetrahedral metal–ligand cluster **46** in the aqueous phase; d) the cylindrical capsule **18** is able to prevent reactions of the shape-complementary guest benzoyl peroxide (**76**) even at elevated temperatures for prolonged periods of time, even though the capsule structure is maintained entirely through hydrogen bonds.

clic trimer had not been observed. Evidence for encapsulated cyclic trimer **74** is provided by NMR spectroscopy, mass spectrometry, and, for **74c**, X-ray crystallography.^[111] In all cases, the trimer is formed as the C_3 -symmetric all-*cis* isomer. The reactivity of **74** is greatly attenuated by encapsulation. No change in the complex is observed for over one month in neutral aqueous solution; the guest also survives the acidic conditions ($\text{pH} < 1$) required for the isolation of the complexes. Again, the guest is too large for formation outside the capsule; instead, the polycondensation process that traps this reactive intermediate must take place within the confines of the capsule walls.

The tetrahedral metal clusters of Raymond and co-workers^[101] offer a radical approach for the stabilization of reactive intermediates. The treatment of a solution of Ga–catecholate based capsule **46** (Figure 15) in D_2O with PEt_3 resulted in the observation of new signals for encapsulated guest in the ^1H and ^{31}P NMR spectra. These signals did not correlate with the expected encapsulation of PEt_3 , but instead can be attributed to the encapsulation of the cationic phosphane–acetone adduct $[\text{Me}_2\text{C}(\text{OH})\text{PEt}_3]^+$ (**75**) that arises as a consequence of the presence of adventitious acetone remaining from the synthesis of capsule **46** (Figure 30c).^[146] This adduct has been previously synthesized under anhydrous conditions, but decomposes rapidly in aqueous solution as a result of the low concentration of acetone. It is likely that **75** forms upon entry of protonated phosphane into a cavity already contain-

ing residual acetone. To confirm the structure of the encapsulated species, $[\text{Me}_2\text{C}(\text{OH})\text{PEt}_3]\text{Br}$ was prepared under anhydrous conditions and added to the capsule in CD_3OD . The resulting ^1H and ^{31}P NMR spectra agreed with those obtained previously in D_2O . Mass spectrometric studies of the methanolic solution provided further evidence for the composition of the encapsulated species.

Even capsules constructed through relatively weak hydrogen bonds can act to stabilize reactive species through encapsulation. Benzoyl peroxide (**76**) readily undergoes homolytic bond cleavage at room temperature to give reactive radical species that are commonly used for the initiation of radical chain reactions or the oxidation of various substrates. The size and shape of **76** make it an excellent guest for capsule **18** (Figure 30d).^[147] A variety of agents normally reactive to **76** at room temperature undergo no detectable reaction in the presence of the preformed encapsulation complex of **76** and **18** during prolonged heating at 70°C . The addition of a small amount of DMF disrupts the hydrogen bonds responsible for encapsulation and results in immediate reaction of the reporter molecules with **76**. Likewise, the addition of a competing guest molecule that displaces **76** from the capsule also results in the release of the reactive species and the onset of oxidation or chain reactions. Studies on complexes of other guests with **18** indicate that the partial opening of the capsule walls is probably responsible for the rapid exchange of small guests, but little is known about the exchange of large rod-shaped guests. Perhaps the complete dissociation of the complex—a rare event—is required. The surprising stability of this complex highlights the subtle effect of shape-selective host–guest interactions on guest-binding and -exchange processes.

6. Summary and Outlook

The final paragraph of a review asks the writer to predict the future—or worse, to tip his hand about the direction his own research will take. Naturally, we are hesitant to do either, but we confess an interest in the construction of synthetic systems that possess nonlinear properties such as autocatalysis and chemical amplification. These characteristics are integral properties of living systems, and they give rise to desirable behaviors such as increased sensitivity, responsiveness, and self-replication. Other questions that remain to be answered lie in the realm of supramolecular mechanisms. In simple encapsulation complexes, an understanding of paired receptor and guest movement during binding and release events is attainable, whereas in the biological realm of complex receptor–ligand systems the flexibility and intricate movement of a receptor and guest during a binding event are difficult to study, and are often overlooked.^[148] The study of simple systems does not limit the details of questions that may be asked, instead, exploring well-defined systems can allow for the understanding of intricacies that otherwise may not even be considered.

We emphasize that reversible encapsulation is not intended as a model of anything; it provides the current outlet for our curiosity about the nature of intimate molecular relationships

and their manipulation. Yet we cannot deny that the compelling nature of encapsulation has its roots in biology. There, compartmentalization provides ways to separate incompatible reagents and environments (endosomes and mitochondria isolate media of widely differing pH values). We believe that reversible encapsulation can provide a probe operating at the boundary of chemistry with biology, the most intriguing of which is how the former gave rise to the latter—the “West Coast” approach to chemical biology. Given the activity at The Skaggs Institute,^[15, 149, 150] the Scripps Oceanographic Institute,^[151] the University of California at San Diego,^[152] and the Salk Institute,^[9] what better location is there to explore this question than La Jolla?

This review is dedicated to Ivar Ugi, the architect of Molecular Diversity. The authors thank Dr. Lubomir Sebo for expert assistance with graphical design and the Skaggs Institute for Chemical Biology for funding. F.H. thanks the NSERC for a graduate fellowship.

Received: June 25, 2001 [A 480]

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Protein-Inspired Materials: Synthetic Concepts and Potential Applications**

Harm-Anton Klok*

Introduction

Natural materials in many cases surpass their synthetic counterparts developed by mankind. Enzymes, for example, can catalyze chemical reactions under physiological conditions with yields and stereoselectivities unmet by synthetic catalysts. From a synthetic point of view, the structural and functional diversity of natural proteins is particularly impressive if one recalls that they are prepared from a limited pool of α -amino acids. Over many years of evolution, nature has developed ingenious methods to prepare perfectly monodisperse polypeptides with excellent control of the primary structure. After synthesis, the linear chains fold and assemble through a number of hierarchical steps into stable and active proteins. This process, as well as the structure and properties of the final protein, are largely determined by the peptide's primary structure.

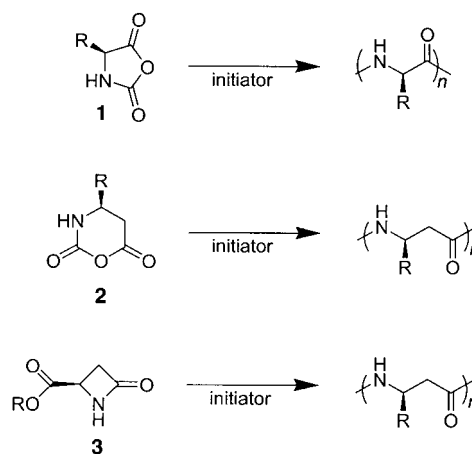
From a materials science point of view polypeptides offer many advantages over conventional synthetic polymers. In particular, their inherent ability to adopt stable conformations and self-assemble into precisely defined structures might allow unprecedented control over materials morphology and properties. Synthetic strategies for the preparation of polypeptides can be divided in three classes:

- ring-opening polymerization,
- solid-phase synthesis,
- protein engineering.

Recent advances in these methods have allowed the preparation of (poly)peptides and (poly)peptide hybrids, which can be assembled in a controlled fashion into supra-molecular architectures and materials that mimic the structure and function of proteins. This article will highlight some recent examples and discuss the current scope and limitations of the different synthetic methods for the preparation of protein-inspired materials.

Ring-Opening Polymerization

Polypeptides can be prepared by ring-opening polymerization of α - and β -amino acid *N*-carboxyanhydrides (α - and β -NCAs, **1** and **2**, respectively)^[1] and β -lactams **3**^[2] (Scheme 1). Whereas polymerization of **1** affords poly-(α -amino acid)s, **2** and **3** yield poly(β -amino acid)s. Generally, the ring-opening polymerizations can be performed following well-established protocols, thus allowing a straightforward synthesis of high molecular weight polypeptides. These polymers, however, are neither monodisperse, nor possess the sequence specificity of natural proteins. In addition, the polymerizations are usually plagued by side reactions, which make it difficult to prepare optically pure polypeptides with predictable molecular weights and narrow molecular weight distributions and also hamper the formation of well-defined block copolymers.



Scheme 1. Strategies for the preparation of polypeptides by ring-opening polymerization.

A number of the drawbacks mentioned above have been overcome since the discovery of a number of transition metal initiators including for example, [bpyNi(cod)] (cod = cycloocta-1,5-dienyl, bpy = 2,2'-bipyridyl) and [Co(PMe₃)₄], which have allowed the synthesis of α -amino acid homo- and block copolymers with unprecedented control of the chain length and very narrow polydispersities.^[3] β -NCAs (**2**) can also be polymerized using nickel amidoamidate com-

[*] Dr. H.-A. Klok
Max-Planck-Institute for Polymer Research
Ackermannweg 10, 55128 Mainz (Germany)
Fax: (+49) 6131-379-100
E-mail: hak@mpip-mainz.mpg.de

[**] The author is grateful to the Deutsche Forschungsgemeinschaft for financial support within the Emmy Noether Programm and to Prof. Klaus Müllen for his continuous interest and support.

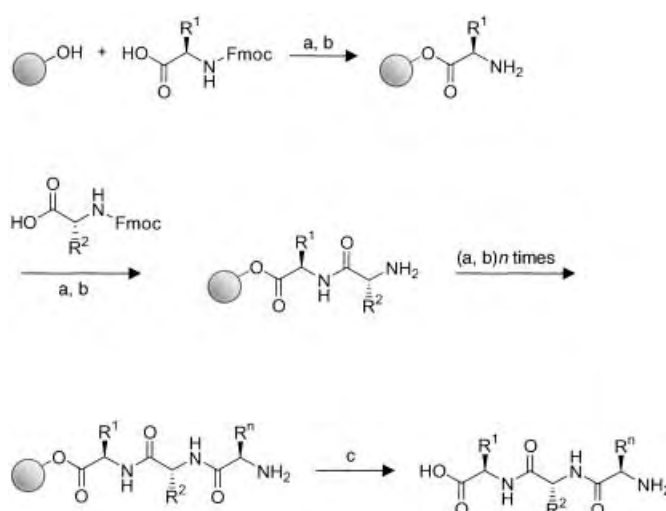
plexes, however, precipitation of the polymers from the reaction mixture was found to limit the molecular weight.^[4] Generally, high molecular weight poly(β -amino acid)s are only accessible by ring-opening polymerization of β -lactams.^[1a, 2] Very recently, it was shown that [Sc(N(TMS)₂)₃] (TMS = trimethylsilyl) can initiate the living polymerization of certain β -lactams, and allows the preparation of unprecedented di- and triblock poly(β -amino acid)s in high yields and with narrow molecular weight distributions.^[5, 6]

The advances in α -NCA polymerization have found application in the biomimetic synthesis of ordered silica structures. Well-defined block copolymers of L-cysteine and L-lysine were found to self-assemble in ordered aggregates, which simultaneously could hydrolyze tetraethoxysilane (TEOS) and direct the morphology of the resulting silica structures (Figure 1).^[7] The design of these block copolymers, which mimic the protein silicatein, was based on the rationale that their amphiphilic character would provide the self-assembling properties while the L-cysteine residues would enable hydrolysis of the TEOS precursor at a neutral pH value. Cross-linking of the block copolymers, by oxidation of the SH groups, affects the self-assembly process and provides an additional means to direct the mineralization process.

Solid-Phase Synthesis

Solid-phase peptide synthesis (SPPS, Scheme 2) is a powerful method for the preparation of small and medium-sized peptides.^[8] In contrast to the NCA polymerization, SPPS allows the preparation of monodisperse peptides with precise control of the primary structure. However, although the yields in each of the reaction steps are very high (>98%), they are not quantitative, which results in the formation of deletion sequences. The concentration of these defects increases exponentially with chain length, and for very large peptides they can constitute the major part of the crude product. As a consequence, small and medium-sized peptides are easily obtained in high yields and purities, however, yields rapidly drop and purification becomes more difficult with increasing chain length.

One way to overcome the limitations of SPPS with respect to the size of the peptides that can be prepared is the thioester-mediated native chemical ligation (NCL) of unprotected peptide segments.^[9] This method (Scheme 3) relies on the chemoselectivity of the reaction between a peptide- α -thioester and another segment containing an N-terminal



Scheme 2. Solid-phase peptide synthesis: a) coupling, b) deprotection, c) cleavage from resin (Fmoc = 9-fluorenylmethoxycarbonyl).

cysteine residue. NCL has been successfully used for the total chemical synthesis of a variety of proteins. Since the peptide segments, which typically contain 50–60 α -amino acids, are prepared by standard SPPS, NCL is a very versatile method that allows the site-specific incorporation of unnatural structures that cannot be introduced or are only difficult to introduce by other techniques.

Recently, protocols have been developed that allow NCL to be carried out on solid supports.^[10] This procedure does not only simplify the purification of the resin-bound product, but also provides a facile route for the synthesis of proteins composed of a larger number of peptide segments. Another very recent highlight is the development of the 1-phenyl-2-sulfanylethyl auxiliary group which obviates the need for a cysteine residue in one of the peptide segments.^[11] In this way, the total synthesis of cytochrome b562, a 106 α -amino acid sequence lacking cysteine, has yielded the correctly folded and functional protein.^[12]

Chemoselective ligation of unprotected peptide segments has also been used for the preparation of template-assembled synthetic proteins (TASPs)^[13] and multiple antigen peptides (MAPs).^[14] The TASP concept focuses on bypassing the protein folding problem by ligating secondary structural elements onto regioselectively addressable topological templates in a predetermined packing arrangement.^[13] MAPs are composed of a large number of peptide epitopes ligated onto a dendritic scaffold and have attracted attention for the development of vaccines.^[14]

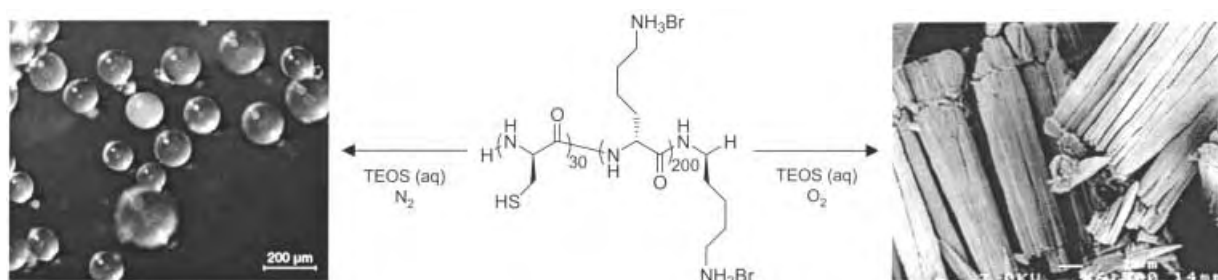
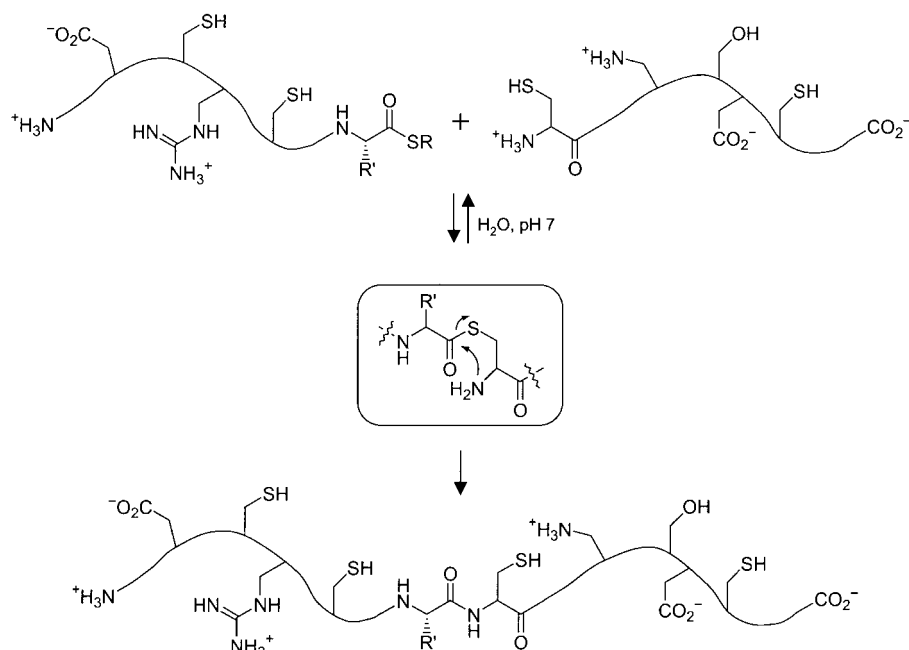


Figure 1. Biomimetic synthesis of ordered silica structures. The size and shape of the silica particles is controlled by the peptide block copolymer.



Scheme 3. Coupling of deprotected peptide segment by NCL.

SPPS has also gained interest for the synthesis of peptide building blocks for biologically inspired supramolecular architectures. Examples include cyclic peptides, which can self-assemble into nanotubes,^[15] and linear oligopeptides that form fibrillar β -sheet structures.^[16] In some cases, the self-assembly of β -sheet-forming peptides can be induced by changes in ionic strength and lead to the formation of hydrogels.^[17] Very recently, the self-assembly properties of such peptides have been combined with the release properties of certain stimuli-sensitive liposomes to allow temperature- or light-induced formation of hydrogels.^[18] Exposure of an aqueous suspension of CaCl_2 -loaded liposomes and the β -sheet-forming peptide to near-infrared light or an increase in the suspension's temperature to 37°C triggers release of CaCl_2 from the liposomes and results in rapid gelation.^[18]

SPPS is also useful for the synthesis of hybrid molecules containing, for example, hydrophobic alkyl chains. Such peptide amphiphiles are interesting since their self-assembly is not only determined by the peptide's primary structure but also by the overall molecular geometry. This effect was nicely demonstrated in a very recent report which describes the self-assembly of peptide amphiphiles into nanofibrous scaffolds with diameters of 6–7 nm.^[19] The formation of the nanofibers was found to be a reversible process that could be controlled by the pH value. Oxidation of the cysteine SH groups in the peptide sequence covalently captured the supramolecular object and resulted in a polymeric nanofiber with a molecular weight of about 2×10^8 Da. The fibers were able to direct the mineralization of hydroxyapatite in the same way as that known for collagen fibrils in bone.

Protein Engineering

Although strategies for cloning and expression of genes have been established for many years and are routinely used in biochemistry and molecular biology, these methods have

been recognized as interesting tools for the preparation of polypeptide materials only in the past 5–10 years.^[20] An overview of the different steps involved in the synthesis of polypeptides by bacterial expression of artificial genes is shown in Figure 2. This strategy, which is also referred to as protein or genetic engineering, is very attractive, since it allows the preparation of high molecular weight and perfectly monodisperse polypeptides with a precisely defined primary structure. Such materials cannot be prepared using the ring-opening polymerization and solid-phase methods discussed above. Protein engineering has been successfully used both for the synthesis of structural proteins such as silk, collagen, and elastin, as well as for the preparation of de novo designed proteins, that is, proteins which are not based on a natural α -amino acid sequence but are designed from scratch.^[20]

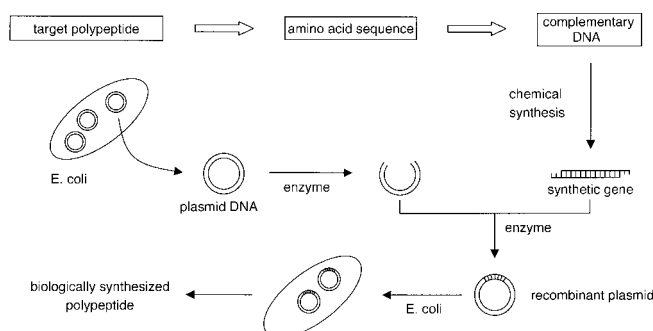


Figure 2. Protein biosynthesis by bacterial expression of artificial genes.

Protein engineering is not restricted to proteogenic α -amino acids. Various methods are available that allow the incorporation of unnatural analogues.^[21] In this way, it has become possible to prepare artificial proteins that carry a variety of nonproteogenic functional groups. A very interesting example is the incorporation of trifluoroleucine (Tfl) in leucine-zipper proteins.^[24] The primary structure of a leucine-zipper protein is characterized by a heptad periodicity *-abcdefg-*, where positions *a* and *d* are occupied by hydrophobic α -amino acids and leucine (Leu) is the predominant α -amino acid at position *d*. Leucine-zipper proteins can form amphiphilic α -helical secondary structures, in which the α -amino acids at positions *a* and *d* constitute the hydrophobic face of the α -helix. Aggregation of two or more of these proteins in a superhelical fashion through the formation of a hydrophobic interhelical interface results in a structural motif referred to as a coiled coil. The folding and assembly of leucine-zipper proteins into coiled-coil structures is a reversible process, which can be controlled by temperature and/or pH values. The replacement of the proteogenic Leu by Tfl

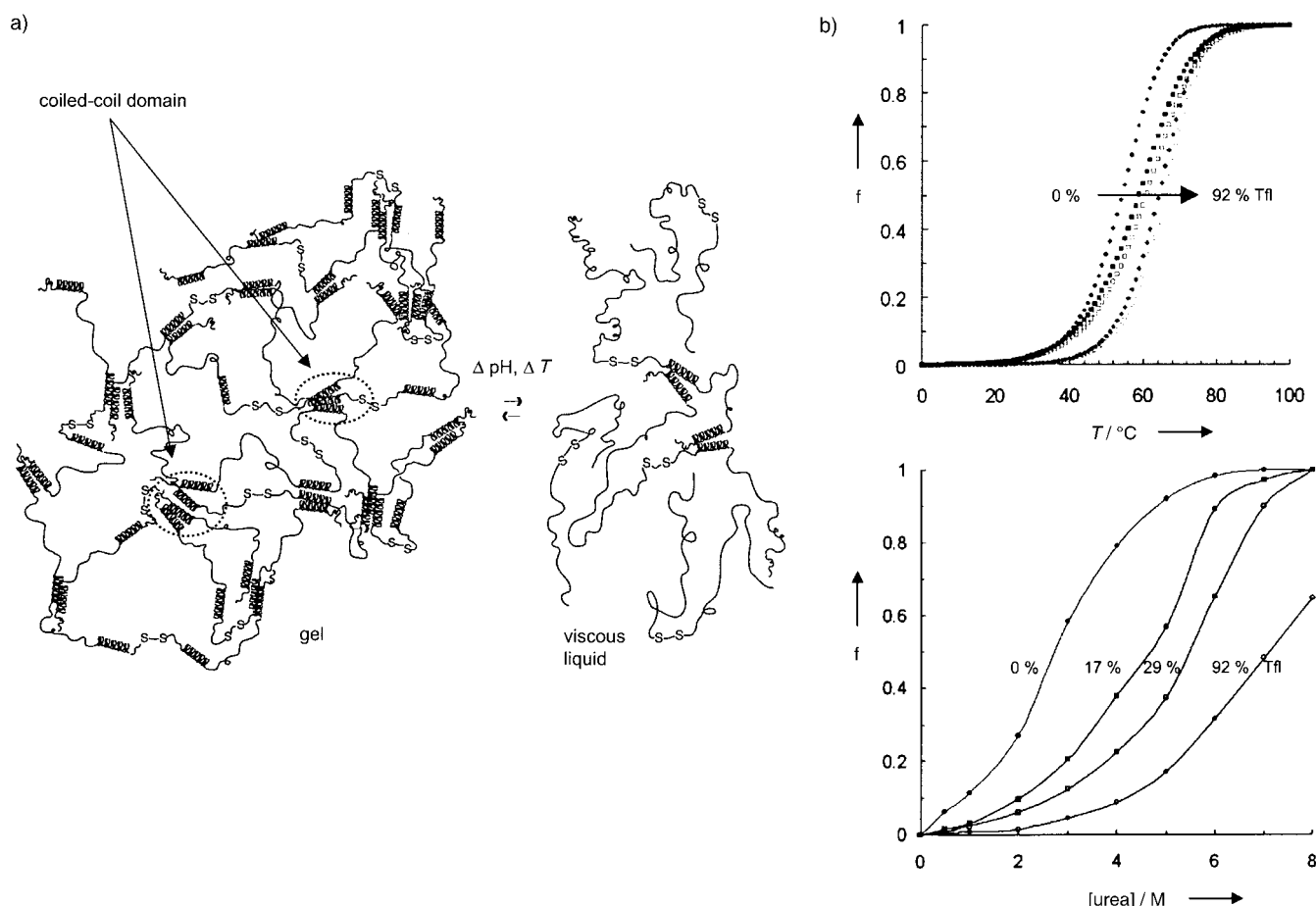


Figure 3. a) Reversible network formation by aggregation of leucine-zipper domains in artificial proteins. b) The thermal (top) and chemical (bottom) stability of the leucine-zipper domains can be enhanced by substitution of leucine for trifluoroleucine (Tfl). (f = fraction unfolded.)

resulted in an elevation of the thermal unfolding temperature by up to 13 °C and an increased resistance against chemical denaturation by urea (Figure 3).^[24] This observation is of particular interest in the context of an earlier finding that artificial protein triblock copolymers containing terminal leucine-zipper domains can form reversible hydrogels.^[25] It is clear that the incorporation of unnatural α -amino acids such as Tfl offers unprecedented opportunities to adjust the sol–gel behavior of these polymers and allows a precise tailoring of the materials properties for specific applications.

Although the control over folding, assembly, and properties exhibited by natural proteins remains to be surpassed, the advances in chemical and biological synthesis outlined above allow hitherto unprecedented control over composition, structure, and organization of artificial proteins and peptide hybrid materials. Undoubtly, these developments and future advances will allow the integration of biological design concepts in materials science and lead to protein-inspired materials with a level of structural control approaching that of natural proteins.

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Of Molecular Gyroscopes, Matroshka Dolls, and Other “Nano”-Toys

Christoph A. Schalley*

At the outset, let us stand up for playing. Often mistaken for a kid's domain, playing opens up new fields of experience even for the “grown-ups”. Possibly, it is one of the prerequisites of the creative process, in the sense that dealing playfully with known ideas provides new ways of thinking. Scientists are no exception. On the contrary, in the area of supramolecular chemistry, with all the model-like realizations of macroscopic objects at a molecular level, the drive to play seems to be followed strongly.

That said, it is no surprise that second-sphere supramolecular complexes, that is, the inclusion of a guest in a host which is already encapsulated in an even larger host, have been compared to russian Matroshka dolls. However, such architectures have been realized only rarely so far, probably because of the difficulties inherent in the synthesis of appropriately sized host molecules which can incorporate an entire host–guest system. Several early examples have been observed by Vögtle and Müller, who described the co-crystallization of γ -cyclodextrin with coronates and cryptates in 1:1 and 2:1 ratios.^[1] These so-called “cascade complexes” contain an alkali metal ion bound inside a crown ether or a cryptand, which—as later shown by X-ray crystal structure analyses^[2]—are surrounded by one or two cyclodextrin molecules. Recently, a few other examples have been added, for example, hydrogen-bonded capsules which self-assemble reversibly in solution around an encapsulated cryptate (Figure 1)^[3] as well as onionlike arrangements of fullerenes and carbon nanotubes.^[4]

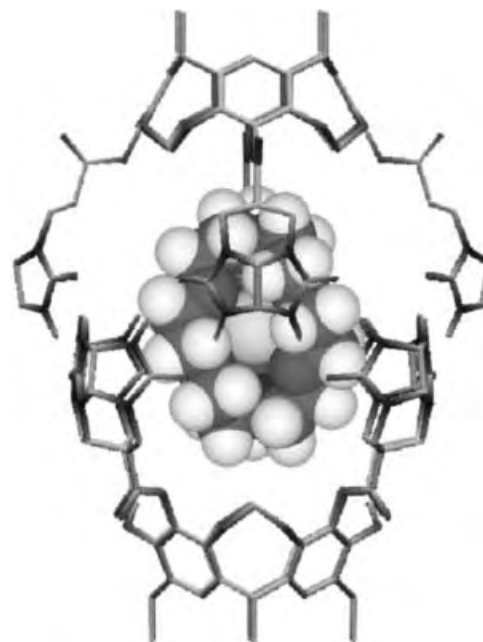


Figure 1. A dimeric, hydrogen-bonded capsule with an interior volume of almost 1000 Å³ which reversibly encapsulates different cryptates in solution. The guest is depicted as a space-filling model (central sphere = K⁺ ion inside the [2.2.2]cryptand), while the capsule is shown as tubes (for clarity, the solubilizing side chains have been omitted).

A particularly beautiful example has just been published by Day, Blanch, and co-workers.^[5] This “gyroscane” (Figure 2) consists of a cucurbit[5]uril that is surrounded by a larger analogue, cucurbit[10]uril.^[6] The particular aesthetics of this complex arise from the fact that both shells belong to the same class of compounds and thus provide a highly symmetrical compound. Upon crystallization from concentrated hydro-

[*] Dr. C. A. Schalley
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)
Fax: (+49) 228-735662
E-mail: c.schalley@uni-bonn.de

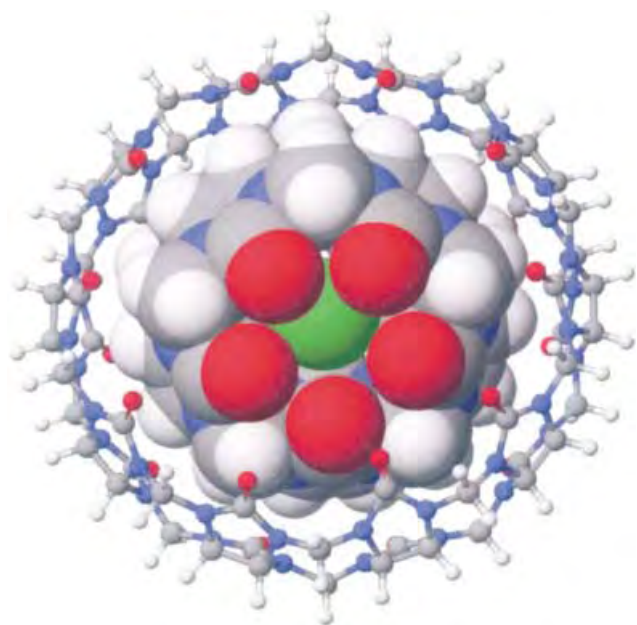


Figure 2. The cucurbit[5]uril inside the cucurbit[10]uril gyroscane encapsulates a chloride ion upon crystallization from concentrated HCl.

chloric acid, the inner cavities of these complexes are filled with a chloride ion, while water molecules or H_3O^+ ions cover the two portals of the inner cucurbituril and bridge the rims of the two macrocycles by hydrogen bonding. The plane of the inner ring is tilted significantly (64°) against that of the outer macrocycle.

The molecule-in-molecule-in-molecule motif is not the only characteristic feature of this arrangement of the two rings. An almost completely free motion of the smaller cycle within the larger one can be demonstrated by ^1H and ^{13}C NMR spectroscopy and computer modeling studies. Both rings can rotate relative to each other in the same plane, but the rotational axis of the inner cucurbituril can also be tilted against that of the outer cucurbit[10]uril macrocycle. This special kind of unprecedented mobility probably emerges from a combination of the rigidity of the glycoluril subunits and their concave curvature perpendicular to the planes of the macrocycles. It is analogous to that of a gyroscope (Figure 3) and consequently led to the authors' suggestion to coin this type of complex "gyroscane". Gyroscopes are not only known as toys. They are also used for precise measurements of rotational movements and serve as means of stabilization in space stations such as the legendary MIR. At the same time, the inner macrocycle is mechanically trapped inside the outer ring: While the rotations inside the cavity are fast on the NMR time scale and provide averaged signals, the exchange of cucurbit[5]uril against a ^{13}C -labeled analogue added to the sample solution proceeds relatively slowly and requires about one hour. These properties place the gyroscane in a series with other "molecular machines",^[7] for example, the "turnstile" described by Bedard and Moore,^[8] the Kelly "ratchet",^[9] or Feringa's overcrowded, light-switchable (*cis/trans*) double bonds that are appropriately equipped with chirality elements to provide unidirectionality (Scheme 1).^[10] Other molecular machines utilize rotaxanes for rotational and shuttling motion; a recent example is shown in Scheme 2.^[11]

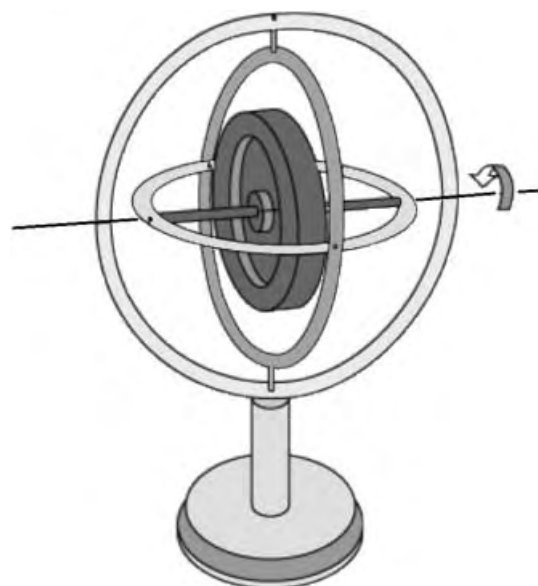
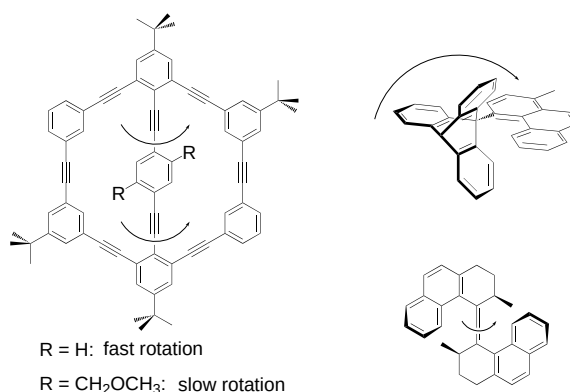
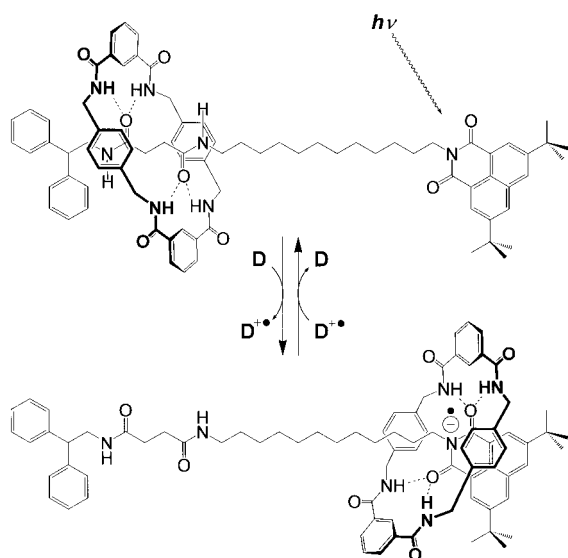


Figure 3. In a gyroscope, the macrocyclic precursor of the gyroscane, the central wheel can rotate freely. When the wheel spins, the conservation of angular momentum prevents the axis from changing its direction even if the framework is moved.



Scheme 1. Molecular turnstile (left), ratchet (top right), and overcrowded double bond (bottom right) as miniature machines. The arrows indicate the rotation of the respective molecule parts. In the example shown at the right side, unidirectionality can be induced by the implementation of suitable chirality elements.

As a third topic, the synthesis is briefly discussed. At first sight this appears to be rather unspectacular, since formation of gyroscane proceeds with low selectivity and a lot of side products. Also, the acid-catalyzed condensation of formaldehyde and glycoluril is easily explained with respect to its mechanism. However, this seemingly boring facade hides at least one intriguing aspect: A mere statistical inclusion of the smaller ring would be so unlikely that there must be a better explanation for the formation of gyroscane. On one hand, the reversible exchange of the cucurbit[5]uril inside the cavity against a free, isotopically labeled analogue is feasible, even if it is only slow. Thus, the exchange barrier is low enough to make the gyroscane a kinetically labile species. On the other hand, NMR experiments, even after longer time intervals, show no sign of cucurbit[5]uril being liberated from the complex. Consequently, the formation of gyroscane is ther-



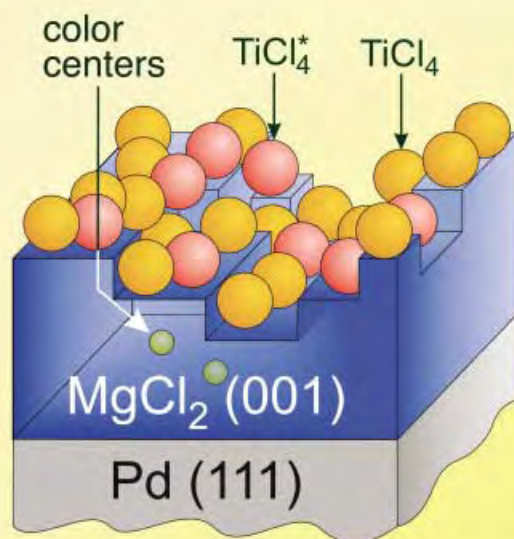
Scheme 2. A light-driven molecular shuttle. **D** corresponds to an electron donor present in solution.

modynamically favorable and the binding constant must be high; the authors report a value of $>10^6 \text{ M}^{-1}$. Rather strong noncovalent binding interactions between the two macrocycles must exist; the encapsulation is thus not purely mechanical. One can easily speculate that the same intermolecular forces already play a pivotal role during the formation of gyroscane, which would then proceed through template control.^[12] The generation of linear, not yet cyclized oligomers would then (among others) yield 10-mers, which could wrap around a cucurbit[5]uril macrocycle and place the ends to be connected in proximity. The ring closure of the large ring would then be favored. In this respect, highly interesting questions remain that invite a more detailed study of the gyroscane: What is the nature of the noncovalent forces between the two rings? What is the exact mechanism of the formation of gyroscane? Which template is involved? Are there other analogous compounds with different ring sizes or is the combination of cucurbit[5]uril and cucurbit[10]uril the only one with a suitable size complementarity?^[5b]

The gyroscane example demonstrates how dealing playfully with chemistry and even the reconstruction of toys and macroscopic machines from everyday life at the molecular level leads to thrilling chemical problems. Finding solutions often leads to a significant increase in our chemical knowledge. Furthermore, the clear visible trend from structural chemistry to the implementation of function also becomes

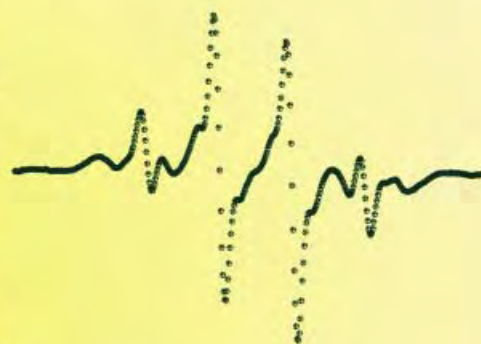
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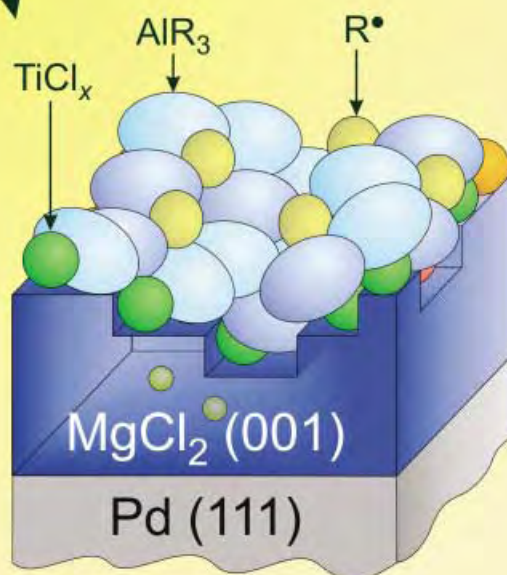


The activation of the titanium centers of a heterogeneous Ziegler–Natta catalyst with trimethylaluminum (AlMe_3) leads to the formation of meta-stable alkyl radicals as reaction intermediates.

+ AlR_3 ,
40 K



The formation of ethyl radicals was observed at low temperatures by in situ ESR spectroscopy.



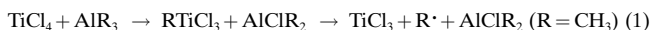
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see the following pages.

Direct Observation of Radicals in the Activation of Ziegler–Natta Catalysts**

Thomas Risse,* Jörg Schmidt, Heiko Hamann, and Hans-Joachim Freund

Dedicated to Professor Georg Hohlneicher on the occasion of his 65th birthday

Since the discovery of low-pressure ethene polymerization by Karl Ziegler and Giulio Natta in 1953 and 1954, several generations of catalysts have been developed which exceed the activity and selectivity of the original catalysts by several orders of magnitude.^[1, 2] The literature on this topic is huge and is still growing as a result of the development of new generations of catalysts, such as metallocene-/methylaluminoxane-based catalysts. The third generation of catalysts, the basis for the model system used in this study, represents a supported catalyst that was developed in 1975. A detailed understanding of the reaction mechanism, however, lags behind these developments. This occurrence has arisen because of the fact that direct characterization of the catalyst is still a challenge; most of the characterization has been done indirectly by analysis of the polymer products. First attempts to characterize the surfaces of model Ziegler–Natta catalyst systems have been published during recent years by Somorjai and his group.^[3, 4] Ab initio calculations on the structural as well as dynamic aspects of the reaction also gave some insight on the mechanism of the reaction.^[5, 6] In the present study we have used a model system consisting of an epitaxially grown MgCl_2 film onto which TiCl_4 was anchored as the active component. The anchoring process has been studied by electron spectroscopy^[7] and, recently in our group, by ESR spectroscopy, we have shown that surface defects in the MgCl_2 film are crucial in this process.^[8] The key step, however, is the so-called activation of the system by adding a co-catalyst, namely an alkyl aluminum compound (trimethylaluminum (TMA), triethylaluminum (TEA)). In this process it is believed that Ti ions assume a lower oxidation state and when TMA is used radicals ($\text{R}^\bullet$) are created according to Equation (1), whereas the activation with TEA takes place through a disproportionation reaction.^[9–12] So far, however, no convincing direct experimental evidence has been presented for the formation of such alkyl radicals during the activation of the catalyst. Herein we prove for the first time, by ESR spectroscopy, the formation of alkyl radicals.



Before we discuss the main issue of this communication, namely the observation of radicals created in the catalyst

activation process, we briefly summarize the structure and morphology of the pre-activated catalyst. As shown schematically in Figure 1 a, a Pd(111) substrate is covered by a MgCl_2 film in a (001) orientation which grows in a layer by layer

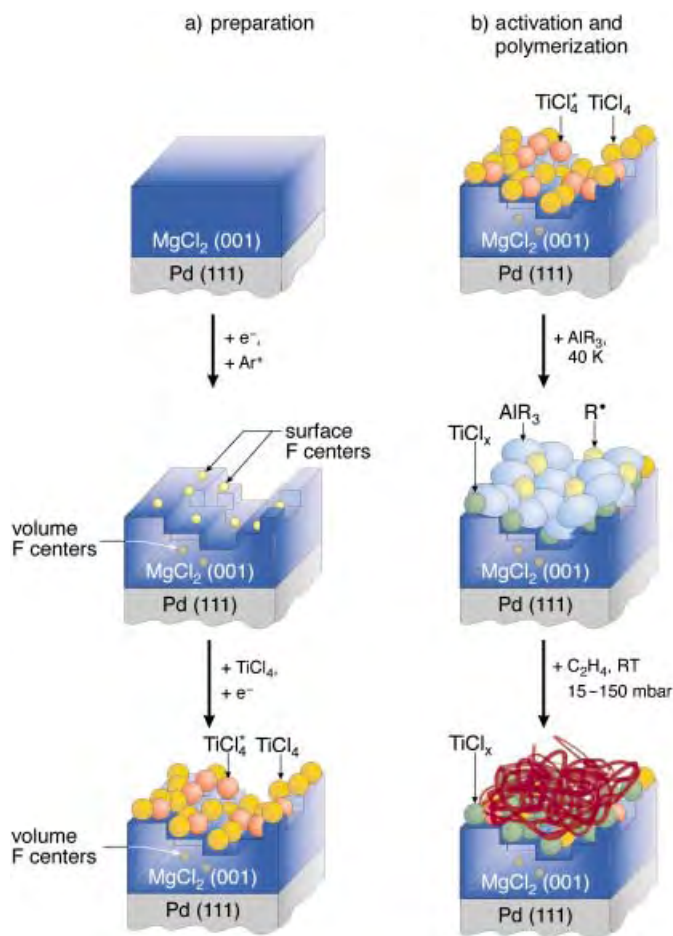


Figure 1. Preparation of the model catalyst. a) Top: preparation of a well-ordered defect-free MgCl_2 film. Center: defect creation by different techniques; color centers are symbolized by yellow spheres. Bottom: anchoring of TiCl_4 ; TiCl_4^* (red) denotes TiCl_4 moieties adsorbed to color centers of the substrate. b) Top: see bottom of part a. Center: adsorption of AlR_3 on the surface at 40 K; alkyl radicals are symbolized by yellow spheres. Bottom: catalyst after polymerization of ethene. TiCl_x (green) symbolizes reduced and perhaps active catalytic sites for polymerization.

mode.^[13] The surface is terminated by chloride ions and the film has a thickness of between 6–12 layers of MgCl_2 , as shown by LEED (Low Energy Electron Diffraction) and Auger spectroscopy. CO adsorption/desorption investigations proved that the film was free of pin holes. In line with the work of Magni and Somorjai, we find that it is necessary to produce defects in the film to bind the TiCl_4 precursor.^[3] We have created defects by various routes, such as by using kinetically controlled growth conditions as well as electron and ion bombardment. A certain class of defects, namely so-called color centers were identified by ESR spectroscopy. When, for example, TiCl_4 was anchored to a film grown under non-equilibrium conditions, 40% of the ESR signal arising from the color center could be quenched by the adsorption of TiCl_4 . This result proves the importance of defects, in this

[*] Dr. T. Risse, Dr. J. Schmidt, Dr. H. Hamann, Prof. Dr. H.-J. Freund
Abteilung Chemische Physik
Fritz Haber Institut der Max-Planck Gesellschaft
Faradayweg 4–6, 14195 Berlin (Germany)
Fax: (+49) 30-8413-4316
E-mail: risse@fhi-berlin.mpg.de

[**] We are grateful to funds from the Ministerium für Wissenschaft und Forschung, NRW, the Deutsche Forschungsgemeinschaft, the Max-Planck-Gesellschaft, and the Fonds der Chemischen Industrie.

particular case color centers, for the adsorption of TiCl_4 on the surface. Since ESR is not an inherently surface-sensitive technique, the result suggests that only part of the color centers really reside at the surface of the MgCl_2 film.

There is evidence in the literature that Ti^{4+} ions are reduced to either Ti^{3+} or Ti^{2+} ions in the process of anchoring TiCl_4 to the $\text{MgCl}_2(001)$ surface. X-ray photoelectron spectroscopy indicates that besides Ti^{4+} , Ti^{2+} is formed exclusively in the model systems.^[7, 14, 15] Our ESR results show that Ti^{3+} centers are formed by electron bombardment, but neither the presence nor the intensity of the Ti^{3+} signal could be correlated with the reactivity of the system towards ethene polymerization. Figure 1a summarizes the various steps described above.

We have activated the $\text{TiCl}_4/\text{MgCl}_2$ system with either TMA or TEA by gas-phase deposition of the components onto the surface at 40 K. The FT-IR spectra of the resulting adsorbate are typical for a condensed film or for matrix-isolated TMA and TEA species, including dimers.

Figure 2 shows ESR spectra after reaction of the TMA with the $\text{TiCl}_4/\text{MgCl}_2$ system. A typical low coverage of TiCl_4 leads to the spectra shown in the upper trace. Increasing the amount of TiCl_4 on the surface by a factor of three increases the

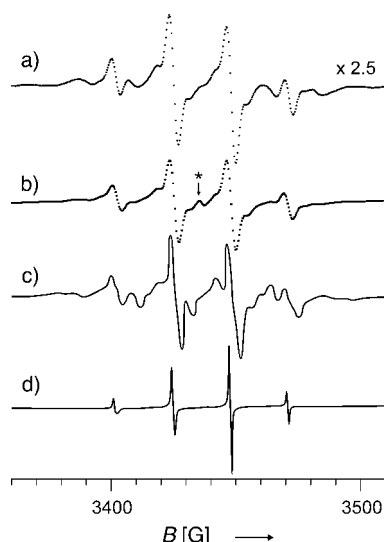


Figure 2. ESR spectra of alkyl radicals taken under various conditions: a) after AlMe_3 is adsorbed at 40 K on a model catalyst with a small Ti content; the spectrum is enlarged by a factor of 2.5 with respect to b); b) after AlMe_3 is adsorbed at 40 K on a model catalyst with three times the Ti content of a), the signal denoted with * is from a background signal; c) ethyl radicals in an ethyl chloride matrix at 77 K;^[17] d) methyl radicals on a silica surface at 77 K.^[16]

intensity of the ESR spectrum by a factor of 1.7, as shown in spectrum b. This correlation between the amount of deposited titanium and the intensity of the ESR signal can be understood by means of an islandlike growth mode of the TiCl_4 on the surface. The spectrum is free of any signal arising from Ti^{3+} ions. This result is in accordance with the literature reports that mainly Ti^{2+} species are formed as a result of the reduction with alkyl aluminum compounds.^[14, 15] Although it might be thought that methyl radicals are the most likely

products in the reduction of a mixed titanium-methyl-chlorine species, a comparison of the spectrum of a methyl radical taken from the literature (see Figure 2d^[16]) with the line shape of the observed spectra clearly reveals distinct differences, thus proving the species formed are not methyl radicals. Whereas the ESR spectrum of a methyl radical is a quartet of lines, the observed spectra show additional multiplet structures around the four dominating lines, which indicates there are further interactions of the unpaired electron relative to those for a methyl radical. By comparison of the line shape to the spectra obtained for other alkyl radicals the present spectrum can be attributed to ethyl radicals. Figure 2c shows for comparison the ESR spectrum of ethyl radicals generated in an ethyl chloride matrix by photolysis.^[17] The line shape of the ESR spectrum of the ethyl radicals can be understood as follows: The unpaired electron on the methylene group couples through a superhyperfine interaction to the three protons of the methyl group, which are magnetically equivalent at this temperature as a result of a fast rotation along the C–C bond, and thus gives rise to a quartet of lines. The two protons of the methylene group, however, give rise to an anisotropic superhyperfine interaction as the adsorption of the molecule on the surface hinders the rotation of the molecule in the laboratory framework defined by the magnetic field. A good description of the observed line shape, as already shown by Shiga et al.,^[16] can be obtained by assuming the anisotropic interaction to be axially symmetric.

There are two key questions that have to be answered:

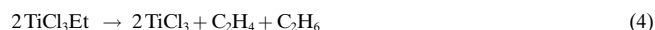
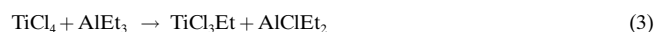
1. Have the radicals been created at the interface between TMA and $\text{TiCl}_4/\text{MgCl}_2$ or in the TMA activating materials?
2. How can it be rationalized that C_2H_5 and not CH_3 radicals have been created?

The first question can be answered by studying the amount of radicals formed as a function of the amount of TiCl_4 at the interface and also as a function of the TMA exposed to the surface. As stated above, the ESR intensity increases as a function of TiCl_4 at low concentrations of TiCl_4 . Most importantly, no radical signal can be observed in the ESR spectrum in the absence of TiCl_4 . Increasing the amount of TMA on the surface results in a saturation of the radical signal. Further evidence for a surface reaction is provided by the observation that the line width of the signal is larger when there is a large amount of titanium on the surface. If it is assumed that radical production occurs at the $\text{TiCl}_4/\text{AlR}_3$ interface, an increase in the number of radicals should also increase the concentration of the radicals close to the interface—these radicals can cause line broadening as a result of dipolar coupling. These observations are compatible with a radical-creation process happening at the interface between TMA and $\text{TiCl}_4/\text{MgCl}_2$, where an alkylation of the TiCl_4 by ligand exchange is supposed to happen. The homolytic bond cleavage that follows this ligand exchange will result in the primary generation of a methyl radical. The size and high mobility, even at low temperature, in the solid state means there are several possibilities for consecutive reactions of this radical.^[18] The most likely reaction that yields ethyl radicals is given in Equation (2). Even though such a reaction has not been investigated so far, it can be crudely estimated that it should be possible from an energetic point of view. The

intensity of the ESR signal of the ethyl radicals is attenuated irreversibly above 50 K and decreases below the detection limit above 80 K. This observation can be explained by assuming that the ethyl radicals diffuse and recombine at these temperatures, as has been observed for methyl radicals above 45 K^[19] and NO₂ radicals on an oxide surface above 75 K.^[20] After heating the surface to elevated temperatures at which TMA desorbs from the surface, carbon is found on the surface; this arises as a result of successful alkylation of the TiCl₄. It is, however, important to note that new C₂H₅ radicals can be created after removing the reacted TiCl_x moieties from the surface, for example, by soft argon sputtering, and redosing with TMA.



An interesting observation is made if TEA is used instead of TMA. Even though the catalyst can be activated with TEA in a similar way as for TMA, ethyl radicals have never been observed. This is in line with a disproportionation reaction proposed in the literature [Eqs. (3) and (4)].



The observation of ethyl radicals in the preceding experiment suggests that these radicals are stable at 40 K, hence the formation of ethyl radicals would undoubtedly lead to an ESR signal. The absence of an ESR spectrum therefore strongly suggests a reaction route which does not involve radicals. This is in accordance with a disproportionation reaction proposed from indirect evidence.^[9–12] The activation is summarized schematically in Figure 1 b. To the best of our knowledge this is the first clear experimental proof for the formation of free radicals in the activation process generated at the interface of a heterogeneous TiCl₄/AlR₃ system.

The model catalyst prepared in this manner does polymerize ethene with high efficiency. The kinetics of polyethylene film growth was followed by in situ FT-IR spectroscopy, and the results, which will be described in detail elsewhere,^[8] are as follows: The polyethylene film created on the surface is partially crystalline with a chain length considerably larger than 20 units. The chains are in a *trans* configuration but do contain some *gauche* defects. The morphology of the MgCl₂ substrate has a strong influence on the growth kinetics of the polymer film: If the substrate is rough the polyethylene film grows in such a way that the ethene can access the reactive interface for comparatively long periods of time, which leads to thick, but rough polymer films. A smooth film, on the other hand, terminates the film thickness very quickly because the polyethylene spreads across the surface and blocks further ethene reaching the reactive interface from the gas phase.

In conclusion, we have prepared an active model Ziegler–Natta catalyst and were able to demonstrate, for the first time, the production of free radicals created at the catalyst interface by in situ ESR spectroscopy, while controlling the preparation of the catalyst by surface science techniques. The model

catalyst polymerizes ethene and the morphology of the catalyst controls the reaction kinetics of the created *trans*-polyethylene film.

Experimental Section

The experiments have been performed in an ultrahigh vacuum (UHV, base pressure: 10^{–10} mbar) apparatus which is described in detail elsewhere.^[8, 21] The apparatus combines ESR with FT-IR spectroscopy and other standard UHV characterization facilities. The Pd(111) single crystal serves as a substrate and is cleaned by sputter/anneal cycles. MgCl₂ was evaporated from a Knudsen cell in a preparation chamber integrated into the apparatus. During evaporation the Pd(111) single crystal was heated to 700 K and treated with MgCl₂ vapor for 30–60 min. The temperature of the Knudsen cell was typically 810 K. After this initial evaporation, the Pd(111) substrate was cooled to 610 K and then exposed to MgCl₂ vapor for several hours (typically 4–5 h). During this procedure we observed an increase in the background pressure up to 10^{–8} mbar as a result of hydrogen evanescence from the MgCl₂ used. The pressure was brought back to the base pressure range by prolonged pumping. Both sides of the Pd(111) crystal have been prepared in this way to increase the sensitivity of the ESR measurements.

For various steps in the preparation of the model catalyst the MgCl₂ films, whose order and composition was controlled by LEED and Auger spectroscopy, could be bombarded with electrons or ions.

The TiCl₄, alkyl aluminum compounds, as well as the ethene were dosed to the surface in the preparation chamber. Details of the preparation and characterization procedures will be published elsewhere.^[8]

Received: November 7, 2001 [Z18180]

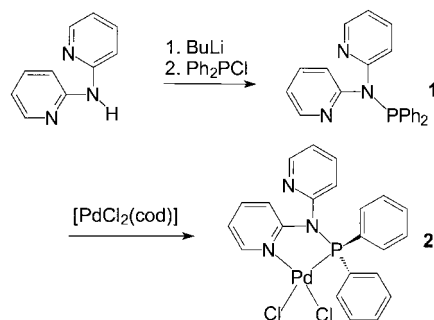
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Combinatorial Libraries with P-Functionalized Aminopyridines: Ligands for the Preparation of Efficient C(Aryl)–Cl Activation Catalysts**

Thomas Schareina and Rhett Kempe*

Today the principles of combinatorial chemistry are used routinely by pharmaceutical companies for the discovery of lead structures.^[1] Recently, these methods have started to find use in such areas as materials science^[2] and catalysis research.^[3] Both in biochemistry and in materials science the methods used have led to an increase in efficiency: by combination of amino acids or nucleotides a plethora of compounds has been generated^[1] with the help of a diverse method repertoire,^[4] and the parallelization or miniaturization of materials-science libraries has resulting in considerable time-saving.^[5] However, in catalyst research the preparation of homogeneous-catalyst libraries with the synthetic strategies of organometallic chemistry gives rise to problems. We report here on a new class of ligands, the P-functionalized aminopyridines, which can be prepared efficiently and in great diversity by use of parallel synthesis under the exclusion of air. These ligands form C(aryl)–Cl activation catalysts for the Suzuki reaction with Group 10 metals.

Di(2-pyridyl)amine reacts with BuLi and chlorodiphenylphosphane to form **1** in high yields (Scheme 1). According to the NMR spectrum, the reaction of **1** with [PdCl₂(cod)] (cod = cyclooctadiene) occurs almost quantitatively to form the complex **2**, the molecular structure of which was determined by X-ray crystallography (Figure 1).^[6] Compound **1** coordinates with the palladium atom to form a five-membered ring. The bond lengths and angles determined for **2** are in agreement with those of other P,N-ligand–dichloropalladium complexes.^[7] Ligands, such as **1** and com-



Scheme 1. Synthesis of **1** and **2**.

[*] Prof. Dr. R. Kempe
Universität Oldenburg
Postfach 2503, 26111 Oldenburg (Germany)
Fax: (+49) 441-798-3352
E-mail: kempe@uni-oldenburg.de
Prof. Dr. R. Kempe, Dr. T. Schareina
Institut für Organische Katalyseforschung
Buchbinderstrasse 5–6, 18055 Rostock (Germany)

[**] We thank the Deutsche Forschungsgemeinschaft, the Bundesministerium für Bildung und Forschung, Degussa AG, the Karl Winnacker Stiftung, the Universität Oldenburg, and the Fonds der Chemischen Industrie for financial support.

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



Figure 1. Molecular structure of **2**. Selected bond lengths [Å] and angles [°]: N1–P1 1.702(5), N2–Pd1 2.053(5), P1–Pd1 2.1951(15), Cl1–Pd1 2.3731(14), Cl2–Pd1 2.303(2); N2–Pd1–P1 83.15(14), P1–Pd1–Cl2 89.52(6), N2–Pd1–Cl1 95.00(14), Cl2–Pd1–Cl1 92.36(6).

plexes or precatalysts, such as **2** should be accessible simply and in large diversity by parallel synthesis.^[8] Many bipyridylamines, 2-aminopyridines,^[9] or similar N-heterocyclic amines can be prepared from primary amines by palladium-catalyzed arylamination.^[10] These may be P-functionalized in parallel in simple synthetic steps and treated with metal salts to form complexes (such as, **1** in Scheme 1). In this way 60 different catalyst systems were synthesized^[11] and tested in parallel in the preparation of 4-cyanobiphenyl from 4-chlorobenzonitrile and phenylboronic acid by the Suzuki coupling.^[12] Selected results are summarized in Table 1. The abbreviations for the

Table 1. Conversions of selected catalyst systems (Suzuki reaction, synthesis of 4-cyanobiphenyl). In total 60 systems were tested.

Entry	Base	Ligand	Catalyst precursor ^[a]	Yield [%]
1	K ₂ CO ₃	B4MPm	[Pd ₂ (dba) ₃]	quant
2	NaOtBu	BPyPy	[Pd ₂ (dba) ₃]	quant
3	NaOtBu	B4MPm	[Pd ₂ (dba) ₃]	quant
4	K ₂ CO ₃	BPyPy	[Pd ₂ (dba) ₃]	83
5	K ₂ CO ₃	TtBP	[Pd ₂ (dba) ₃]	80
6	K ₃ PO ₄	BPy ₂ (o-P)Py	Pd(OAc) ₂	78
7	NaOtBu	DtBPCl	[Pd ₂ (dba) ₃]	76
8	K ₃ PO ₄	PPmPm	[Ni(cod) ₂]	65

[a] dba = dibenzylidenacetone.

ligands used are explained in the box below. One of the best ligands in the palladium-complex-catalyzed Suzuki coupling^[13] is TtBP,^[14] which is reproducibly surpassed by B4MPm.^[15]

Nomenclature of the compounds R₂PNR'R''

R = phenyl (P), cyclohexyl (C), *tert*-butyl (B)
R', R'' = 2-pyridyl (Py), 3-methyl-2-pyridyl (3M), 4-methylpyridyl (4M), 6-methyl-2-pyridyl (6M), 4,6-dimethyl-2-pyridyl (4,6M), 6-methoxypyridinyl (Mx), 2-pyrimidyl (Pm), pyrazinyl (Pa), trimethylsilyl (Si), 4-methylquinolin-2-yl (L), 2-(*N,N*-di-2-pyridyl)phenyl (Py₂(o-P))

Further ligands: tri(*tert*-butyl)phosphane (TtBP), *rac*-2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (binap), 1,3-bis(diphenylphosphanyl)propane (bdpp), di(*tert*-butyl)chlorophosphane (DtBPCl), triphenylphosphane (PPh₃)

In addition to palladium, other metals are also attracting increasing interest for use in C–C coupling, for example, nickel, which is relatively reduction-stable and less expensive.^[16] Thus, the activity of the novel catalysts was also investigated in the nickel-complex-catalyzed coupling of non-activated *p*-chloroanisole with phenylboronic acid to form 4-methoxybiphenyl. Selected results of the 84 screening experiments are summarized in Table 2.^[11] Here too the P-functionalized aminopyridines in combination with nickel and palladium are, under screening conditions, superior to the known catalyst systems.^[14, 17] Remarkably, ligands which in combination with nickel salts act as catalysts show almost no catalyst activity or selectivity with palladium salts and vice versa.^[18]

Table 2. Conversions of selected catalyst systems (Suzuki reaction, synthesis of 4-methoxybiphenyl).

Entry	Base	Ligand	Yield [%] ^[a]	Yield [%] ^[b]
1	K ₃ PO ₄	C46MMx	14	53
2	K ₂ CO ₃	BPmPm (1 equiv)	53	0
3	K ₃ PO ₄	BPmSi	19	31
4	K ₃ PO ₄	TtBP	4	6
5	K ₃ PO ₄	PPh ₃	1	38

[a] With [Pd₂(dba)₃]. [b] With [Ni(cod)₂].

The following may be concluded from these investigations: palladium or nickel complexes which are stabilized by P-functionalized aminopyridines can activate C(aryl)–Cl bonds efficiently and possess a stable metal–ligand bond (formation of a five-membered ring chelate, see Figure 1). This property allows such catalyst systems to couple non-activated chloroarenes with problematic functional groups, that is those which can poison the catalyst. A summary of the 48 screening experiments^[11] on the coupling of 3-chloropyridine to 3-phenylpyridine with phenylboronic acid is shown in Table 3. Complexes with ligands which have established

Table 3. Activation of 3-chloropyridine (Suzuki reaction, synthesis of 3-phenylpyridine). In total 48 systems were tested.

Entry	Base	Ligand	Catalyst precursor	Yield [%]
1	K ₃ PO ₄	B4MPm	Pd(OAc) ₂	90
2	K ₃ PO ₄	B4MPm	[Pd ₂ (dba) ₃]	89
3	K ₃ PO ₄	BPyPy	[Pd ₂ (dba) ₃]	86
4	K ₃ PO ₄	BPaPa	[Pd ₂ (dba) ₃]	79
5	K ₃ PO ₄	B4MPm (0.5 %)	[Pd ₂ (dba) ₃] (0.5 %)	76
6	K ₃ PO ₄	B4MPm (0.25 %)	[Pd ₂ (dba) ₃] (0.25 %)	69
7	K ₂ CO ₃	BPyPy	[Pd ₂ (dba) ₃]	58
8	K ₃ PO ₄	TtBP	[Pd ₂ (dba) ₃]	5
9	K ₃ PO ₄	<i>rac</i> -binap	[Pd ₂ (dba) ₃]	1
10	K ₃ PO ₄	bdpp	[Pd ₂ (dba) ₃]	0

themselves with non-activate chloroarenes (TtBP) or with activated pyridines (2- or 4-chloropyridine; binap, bdpp)^[10] exhibit lower activity than B4MPm or, in some cases, even none. A similar situation occurs in the reaction of 2-chloro-4,6-dimethoxytriazine to 2,4-dimethoxy-6-phenyltriazine with phenylboronic acid (Table 4).

Table 4. Activation of 2-chloro-4,6-dimethoxytriazine (Suzuki reaction, synthesis of 2,4-dimethoxy-6-phenyltriazine, catalyst precursor: [Pd₂(dba)₃]). In total 19 systems were tested.

Entry	Base	Ligand	Yield [%]
1	K ₃ PO ₄	CPmPm	89
2	K ₃ PO ₄	BPaPa	79
3	K ₃ PO ₄	BPmPm	77
4	K ₃ PO ₄	TtBP	72
5	K ₃ PO ₄	<i>rac</i> -binap	47
6	K ₃ PO ₄	bdpp	31

We have thus demonstrated that combinatorial libraries with efficient catalyst systems can be developed for scientifically and industrially important reactions^[19] by using simple synthetic strategies from organometallic chemistry. A broad application of the P-functionalized ligand class may be expected since many homogeneous catalysts with late transition metals contain pyridine and/or phosphane ligands.^[20] The time-saving and simple preparation of the ligands is especially advantageous.

Experimental Section

All reagents are commercially available and were used without further purification. Air- and water-sensitive materials were handled with the exclusion of air and moisture in Schlenk flasks or in a glove box (Braun, Labmaster 130). Solvents (Aldrich and Cambridge Isotope Laboratories) were dried with sodium tetraethylaluminate or molecular sieve (CH₂Cl₂, CD₂Cl₂).

1: Under argon, *n*BuLi (2.5 M, 1.6 mL, 4 mmol) in hexane was added to di(2-pyridyl)amine (0.68 g, 4 mmol) in diethyl ether (10 mL) at –77 °C. After 1 h chlorodiphenylphosphane (0.72 mL, 0.882 g, 4 mmol) in diethyl ether (4 mL) was added dropwise. During the addition the reaction mixture became brilliant yellow. After stirring for 48 h at room temperature the solution was transferred into another Schlenk flask by filtration and evaporated to dryness, the residue extracted twice each time with a mixture of diethyl ether (10 mL) and THF (10 mL). The solvents were distilled off in vacuum into a flask cooled with dry ice and the residue was dried at 1 mbar and room temperature. Yield: 1.42 g (quantitative). Elemental analysis (%) calcd for C₂₂H₁₈N₃P: C 74.35, H 5.11, N 11.82; found: C 74.50, H 5.31, N 11.68; ¹H NMR (C₆D₆): δ = 8.16 (m, 2H), 7.73 (m, 4H), 6.97 (m, 6H), 6.57 (d, 2H), 6.33 (ddd, 2H); ¹³C NMR (C₆D₆): δ = 158.35, 158.29, 148.81, 138.74, 138.54, 136.97, 136.07, 136.06, 133.76, 133.55, 132.04, 128.77, 128.53, 128.11, 118.37, 118.26; ³¹P NMR (C₆D₆): δ = 69.37.

2: Under argon, dichloromethane (4 mL) was added to [PdCl₂(cod)] (0.071 g, 0.25 mmol) and **1** (0.089 g) in a Schlenk flask. After layering with diethyl ether (6 mL) pale yellow crystals were obtained after about 1 week. These were collected by filtration, washed with diethyl ether (4 mL), and dried in vacuum. Yield: 0.10 g (75 %). Elemental analysis (%) calcd for C₂₂H₁₈Cl₂N₃PPd: C 49.60, H 3.41, N 7.89; found: C 49.29, H 3.51, N 7.81; ¹H NMR (CD₂Cl₂): δ = 9.43 (m, 1H), 8.24 (m, 1H), 7.88 (m, 5H), 7.66 (m, 1H), 7.50 (m, 4H), 7.37 (m, 5H), 7.08 (m, 1H), 7.02 (m, 1H), 6.70 (m, 1H), 6.54 (m, 1H); ¹³C NMR (CD₂Cl₂): δ = 150.4, 150.1, 149.1, 140.2, 138.5, 133.4, 133.3, 132.2, 127.8, 127.7, 125.9, 125.3, 122.8, 121.7, 121.7, 120.8, 118.0; ³¹P NMR (CD₂Cl₂): δ = 99.2.

Received: 10 January, 2002 [Z18507]

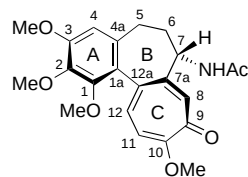
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Facile Construction of the Colchicine Skeleton By a Rhodium-Catalyzed Cyclization/Cycloaddition Cascade**

Timm Graening, Willy Friedrichsen, Johann Lex, and Hans-Günther Schmalz*

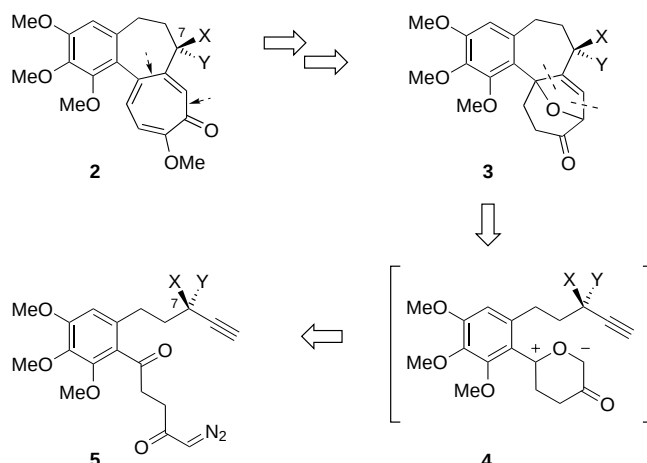
Colchicine (**1**), the major alkaloid of the meadow saffron (*colchicum autumnale*), has long been known for its remarkable antimitotic activity. It is an established drug in the treatment of acute gout and familial mediterranean fever and, moreover, it is currently being tested against a broad variety of other diseases.^[1] The biological activity of **1** mainly depends on its selective binding to tubulin which leads to an inhibition of microtubule formation.^[2] Structural analogues of the natural product are also of great interest, in particular as potential antitumor agents.^[3]



1: (aR,7S)-colchicine

Owing to its biological importance and unique chemical structure, colchicine (**1**) has received considerable attention from synthetic chemists, and several total syntheses of **1** have been elaborated.^[4] During this work, it became apparent that the major difficulty lies in the construction of the troponone ring C, which is condensed to a second seven-membered ring (B). Still, the search for general and practicable synthetic routes towards **1** and structurally related compounds remains an important challenge. We here disclose an unprecedented short and efficient entry to the fully elaborated colchicine carbon skeleton which exploits the synthetic power of a metal-catalyzed domino reaction as the key step.^[5, 6]

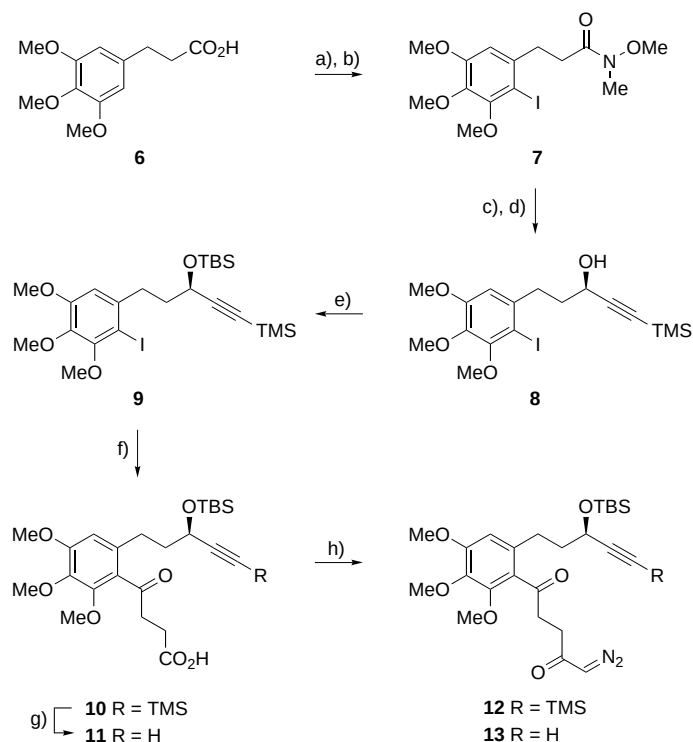
Our retrosynthetic analysis (Scheme 1) was guided by the consideration that it would be, for general strategic (topological) reasons, very attractive to build up the rings B and C simultaneously by an intramolecular cycloaddition (A → ABC approach).^[7, 8] According to the methodology for the synthesis of benzotropolones and heteroanalogues published previously,^[9] it seemed feasible that a troponone of type **2**^[10] could be generated from a precursor of type **3**,^[11] which in turn would be the product of an intramolecular [3+2] cycloaddition of a carbonyl ylide (**4**) formed in situ by rhodium-catalyzed decomposition of an α -diazoketone of type **5**.^[9, 12] The intra-



Scheme 1. Retrosynthetic analysis (X = H, Y = NHR; or X = OR, Y = H).

molecular mode of the cycloaddition step could even permit the use of an *unactivated* acetylene and thus allow prior installation of the stereocenter at position 7.

As a precondition for the investigation of the envisioned key transformation, a synthesis of cyclization precursors of type **5** was developed (Scheme 2). Starting from the commer-



Scheme 2. Synthesis of cyclization precursors: a) (COCl)₂ (1.2 equiv), CH₂Cl₂, 0 °C to RT, 12 h, removal of all volatiles, then NHMeOMe · HCl (1.1 equiv), Py (2.2 equiv), CH₂Cl₂, 0 °C, 1 h; b) Ag(CF₃CO₂) (1.05 equiv), I₂ (1 equiv), CHCl₃, RT, 4 h, 92 % (over two steps); c) DIBAH (1M in THF, 2.5 equiv), THF, –78 °C, 45 min, then CH₃COCH₃, –78 to –20 °C, workup with 0.5M aqueous tartaric acid; d) Cl₂CeC≡TMS (2 equiv), THF, –78 °C to RT, 16 h, 98 % (over two steps); e) TBSCl, imidazole, DMF, RT, 15 h, 93 %; f) *i*PrMgBr (1.7 equiv), THF, –25 °C, 4.5 h, then succinic anhydride (2 equiv), THF, 0 °C, 30 min, 52 %; g) K₂CO₃, MeOH, RT, 3 h, 99 %; h) *i*BuOCOC(=O)Cl (1 equiv), NEt₃ (1 equiv), THF:Et₂O (1:1), –20 °C to –15 °C, then CH₂N₂ (5 equiv), Et₂O, –5 °C, 16 h, 66 % (*rac*-**12**), 70 % (*rac*-**13**). DIBAH = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

[*] Prof. Dr. H.-G. Schmalz, Dipl.-Chem. T. Graening, Dr. J. Lex
Institut für Organische Chemie
Universität zu Köln
Greinstrasse 4, 50939 (Germany)
Fax: (+49) 221-470-3064
E-mail: schmalz@uni-koeln.de

Prof. Dr. W. Friedrichsen
Institut für Organische Chemie
Christian-Albrechts-Universität zu Kiel
Otto-Hahn-Platz 4, 24098 Kiel (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie. The authors thank Dr. H. Schmickler and Dr. M. Schäfer for their invaluable support with advanced NMR and MS techniques. Gifts of chemicals from Chemetall AG are gratefully acknowledged.

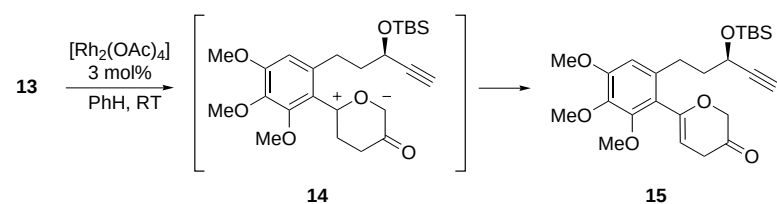
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

cially readily available acid **6**, the bifunctional compound **7** was prepared by converting the acid functionality (via the acid chloride) into the Weinreb amide^[13] and subsequent aromatic iodination using iodine in the presence of silver trifluoroacetate.^[14] To elaborate the “upper” carbon chain, the Weinreb amide was reduced with DIBAH, and the resulting aldehyde was alkynylated by using the reagent prepared from lithiated trimethylsilylacetylene and cerium(III) chloride in THF. The obtained propargylic alcohol *rac*-**8** was then converted into its *tert*-butyldimethylsilyl-protected derivative *rac*-**9** under standard conditions. Following this straightforward five-step sequence, the iodide *rac*-**9** was obtained in 84% overall yield starting from **6**.

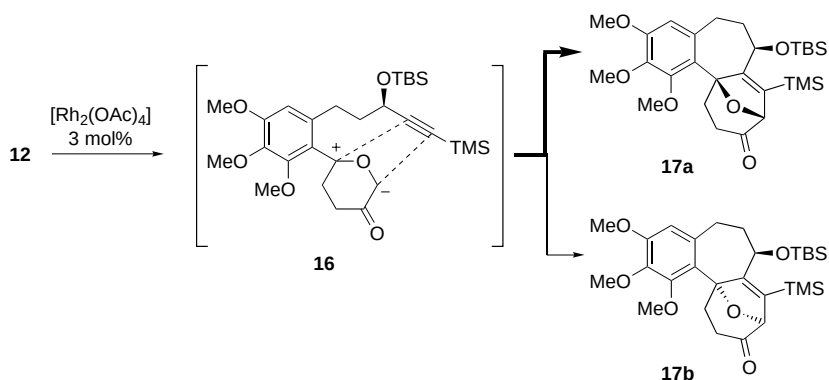
To attach the “lower” 1,4-dicarbonyl chain, the iodide *rac*-**9** was first converted into the corresponding Grignard compound by treatment with isopropylmagnesium bromide at low temperatures.^[15] Addition of the resulting solution to succinic anhydride in THF at 0°C directly afforded the desired 4-ketocarboxylic acid *rac*-**10** in 52% yield. This was transformed into the α -diazoketone *rac*-**12** by reacting the in situ prepared mixed anhydride with an excess of diazomethane.^[12d, 16] Alternatively, the acid *rac*-**11** (obtained from *rac*-**10** by selective desilylation using K₂CO₃ in MeOH) was transformed into *rac*-**13**. The two α -diazoketones *rac*-**12** and *rac*-**13** were obtained as yellow oils after flash chromatographic purification (SiO₂, EtOAc:cyclohexane = 1:1) and directly employed in the cyclization experiments.

When *rac*-**13** was subjected to standard conditions for the Rh-catalyzed generation of carbonyl ylides (3 mol% [Rh₂(OAc)₄], benzene, room temperature)^[12] not even traces of the desired cycloadduct (of type **3**) could be detected in the product mixture. Instead, the enoether *rac*-**15**, arising from simple proton transfer (1,4-H shift) within the intermediate *rac*-**14**, was isolated as the only product in 76% yield (Scheme 3).^[17]

To avoid a possible participation of the relatively acidic alkynyl hydrogen atom in the undesired proton transfer and to promote the cycloaddition step, the silylated α -diazoketone *rac*-**12** was subjected to the same Rh catalyst, but at elevated reaction temperatures. Indeed, when a solution of *rac*-**12** was slowly added to a refluxing solution of 3 mol% of [Rh₂(OAc)₄] in benzene, the cycloadduct *rac*-**17** was formed in 25% yield, and in refluxing toluene an even greatly improved yield of 62% was obtained (Scheme 4). In both cases, the diastereomers *rac*-**17a** and *rac*-**17b** were formed in a 14:1 ratio together with significant amounts of the corre-



Scheme 3. Unsuccessful attempt at the cyclization of **13**.



Scheme 4. Successful cyclization of **12**: a) benzene, reflux, slow addition of *rac*-**12** over 3.5 h, 30 min, 25%; b) toluene, reflux, slow addition of *rac*-**12** over 3.5 h, 30 min, 62% (*rac*-**17a**:*rac*-**17b** = 14:1).

sponding enoether. Evidently, the initially generated ylide *rac*-**16** had now undergone the crucial intramolecular cycloaddition reaction.

Notably, in contrast to earlier reports,^[12b] this demonstrates that the Rh-catalyzed cyclization/cycloaddition methodology can efficiently be used for the construction of ring systems containing two fused seven-membered rings, but only if higher temperatures are employed, which had not been considered as beneficial for such reactions so far.^[12] The relative configuration of the main diastereoisomer *rac*-**17a** was initially secured by NMR-NOE experiments and later confirmed by X-ray crystallography (Figure 1).^[18]

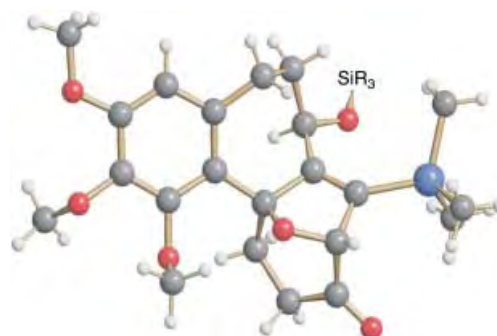


Figure 1. Structure of *rac*-**17a** in the crystalline state. The atoms of the large TBS group are not shown for reasons of clarity.

In conclusion, the advanced colchicine intermediate *rac*-**17** was prepared in only eight steps (18% overall yield) starting from simple and readily available building blocks. The high efficiency of the sequence is available both on a powerful domino reaction and on an economical use of functional groups during the assembly of the cyclization precursor. We are currently focussing on the completion of the synthesis of colchicine (also in the non-racemic series) and on the exploitation of the chosen strategy in the synthesis of new colchicine analogues.

Received: January 15, 2002 [Z18522]

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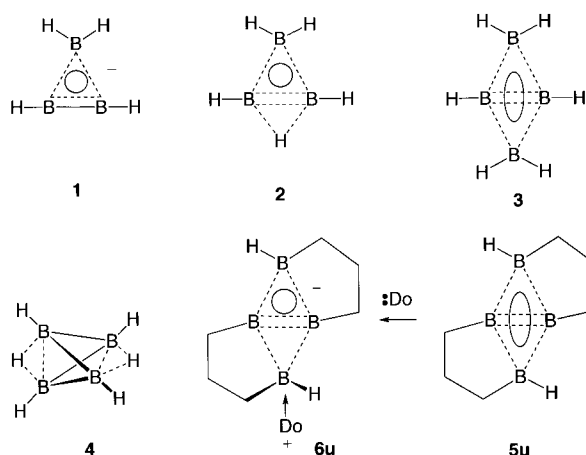
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- [18] For crystal data of *rac*-**17a** see Supporting information. CCDC-177454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Aromatic Boranes with Planar-Tetracoordinate Boron Atoms and Very Short B–B Distances**

Carsten Präsang, Matthias Hofmann, Gertraud Geiseler, Werner Massa, and Armin Berndt*

Dedicated to Professor Anton Meller on the occasion of his 70th birthday

Boranes with planar-tetracoordinate boron atoms have until now only been studied by computations.^[1–3] The prototype of such compounds is anion **1** (Scheme 1), whose planar-tetracoordinate boron atom forms a three-center, two-electron (3c2e) σ bond as well as a 3c2e π bond with the two other boron atoms.^[2] Thus **1** is one of the simplest double

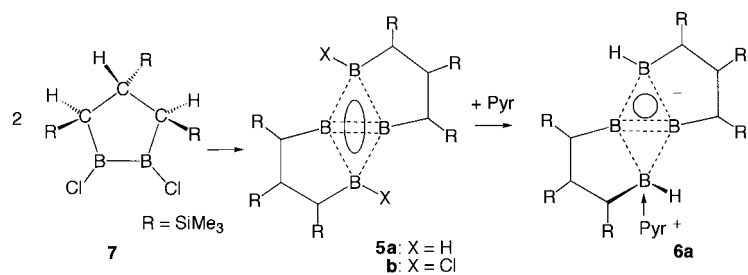


Scheme 1. Borane prototypes **1–3**, **5u**, and **6u** with planar-tetracoordinate boron atoms. Solid lines symbolize 2c2e bonds, triangles drawn with dashed lines 3c2e σ bonds, circles 3c2e π bonds, and ellipsoids 4c2e π bonds. In the distorted tetrahedral **4** the four connecting lines between the boron atoms are drawn to indicate the spatial relationships. In **4** there are ten electrons available to connect the boron atoms. In contrast, in the isomer **3** as well as in **5u** and **6u** there are only six electrons each.

aromatics.^[4] Upon protonation the classical B–B bond in **1** is transformed into a 3c2e B–H–B bond in **2**. However, the double aromatic electronic structure of **1** is retained in **2**. In tetraborane(6) **3**^[5] the hydrogen bond in **2** is replaced by a planar BH₂ bridge.^[6, 7] Known tetraboranes(6) are derivatives of the distorted tetrahedral isomer **4**, which according to computations at the MP2/6-31G* level is 9.2 kcal mol^{–1} lower in energy than **3**.^[5] Here we present **5a** and **6a** (Scheme 2), the first derivatives of the prototypes **5u** and **6u**; both represent

[*] Prof. Dr. A. Berndt, C. Präsang, G. Geiseler, Prof. Dr. W. Massa
Fachbereich Chemie
Philipps-Universität Marburg
Hans-Meerwein-Strasse, 35032 Marburg (Germany)
Fax: (+49) 6421-282-8917
E-mail: berndt@chemie.uni-marburg.de
Dr. M. Hofmann
Anorganisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)

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



Scheme 2. Synthesis of the tetraboranes(6) **5a**, **b** from **7** and of the pyridine adduct **6a** from **5a**; Pyr = 4-*tert*-butylpyridine.

two-electron aromatics. In **6a** one of three boron π centers is planar-tetracoordinate, in **5a** all four are.

The dichlorotetraborane(6) **5b** is formed along with KCl as the sole product upon treatment of 1,2-dichloro-1,2-diborolane **7**^[8] with K/Na alloy in pentane. The tetraborane(6) **5a** results from the reaction of **5b** with two equivalents of NaBEt₃H. The adduct **6a** crystallizes at -30°C from a solution of **5a** and two equivalents of 4-*tert*-butylpyridine in pentane (Scheme 2). Figure 1 shows the structures of **5a** and **6a** in the crystal.^[9] Table 1 compares relevant structural data experimentally observed for **5a** and **6a** with those computed at the B3LYP level^[10] for **5a** and **3** as well as for the adduct **3**·NH₃ (as a model for **6a**). The NMR data for **5a**, **5b**, and **6a** are presented in Table 2.

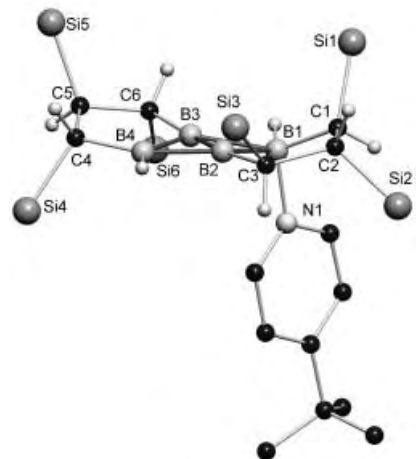
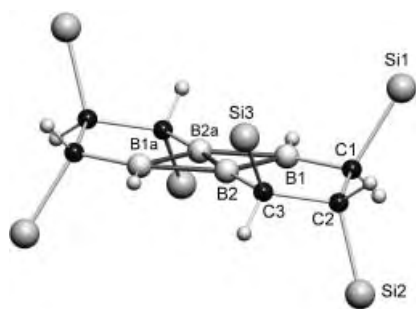


Figure 1. Structures of **5a** (top) and **6a** (bottom) in the crystal; for reasons of clarity the methyl groups of the trimethylsilyl substituents are omitted. Selected bond lengths [pm] and angles $^{\circ}$ (supplementing Table 1): **5a**: B1–H 112.3(17), B1–C1 155.8(2), B2–C3 157.8(2), C1–C2 156.3(2), C2–C3 156.4(2); H–B1–C1 117.7(9), B2–B1–B2a 51.7(1), B1–B2a–B2 64.4(1), B1–B2–B2a 63.9(1), B1–B2–B1a 128.3(1), B1–B2–C3 109.1(1), B2–B1–C1 99.8(1); **6a**: B1–N1 164.9(3).

The boron atoms in **5a** form a diamond with a very short diagonal length of 152.4(3) pm. In the slightly folded (12.8°) pyridine adduct **6a** the corresponding distance is only 151.1(3) pm and thus represents the shortest distance ever measured between two boron atoms.^[11, 12] Even more unusual is the geometry at the corner of the diamond in **5a** and at the noncoordinated corner in **6a**: Both B1 and B1a in **5a** as well as B4 in **6a** have four neighboring atoms in one plane (torsional angles in **5a**: H, B1, B2, B2a $4.3(16)^{\circ}$, C1, B1, B2, B2a $179.4(2)^{\circ}$; in **6a**: H04, B4, B2, B3 $2.7(11)^{\circ}$, C4, B4, B3, B2 $173.9(2)^{\circ}$).^[13] It is also remark-

able that despite the presence of two equivalents of 4-*tert*-butylpyridine, only the monoadduct is formed. Diboranes(4) with four donor substituents (OR or SR) easily add two molecules of 4-methylpyridine.^[14] While the addition of one molecule of 4-methylpyridine to diborane(4) only leads to a modest increase in the B–B distance (by 2.8 pm), the B–B distance in the “pyridine-coordinated” boron triangle B1, B2, B3 of **6a** increases by about 13 pm. In the “non-

Table 1. Selected structural data for **5a** and **6a** (experimental) as well as for **5a**, **3**, and **3**·NH₃ (calcd).^[a]

	5a	5a	3	6a	3 ·NH ₃
B1–B2	175.2(2)	176.3	174.4	188.6(3)	187.0
B2–B1A	174.5(3)	173.3	174.4		
B2–B4				169.7(3)	168.1
B1A–B2A	175.2(2)	176.3	174.4		
B4–B3				169.1(3)	168.1
B2A–B1	174.5(2)	173.3	174.4		
B3–B1				187.4(3)	187.0
B2–B2A	152.4(3)	152.0	153.0		
B2–B3				151.1(3)	150.9
B1, B2, B2A, B1A	180.0	166.4	180.0		
B1, B2, B3, B4				167.2(2)	167.0
B2A–B2–C3	172.9(1)	169.0	–		
B3–B2–C3				171.3(2)	–

[a] Bond length [pm], bond angles $^{\circ}$; see Figure 1 for the numbering of the atoms.

Table 2. Selected physical and spectroscopic properties of **5a**, **5b**, and **6a**.

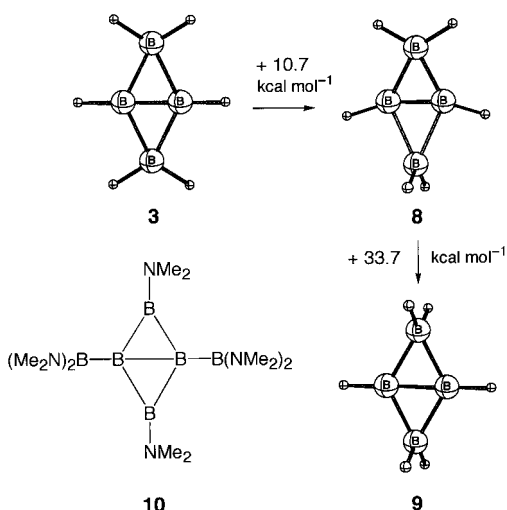
5a: Yellow solid, m.p. 165°C (no decomp), yield 60%; ¹H NMR (300 MHz, C₆D₆, 27°C): δ = 7.00 (br. s, 2H; BH), 2.31 (s, 2H; (B₂H)BCHSi), 2.03 (d, ³J(H,H) = 4.2 Hz, 2H; B₃BCHSi), 1.78 (pseudo triplet, ³J(H,H) = 3.5 Hz, 2H; CHSi), 0.28, 0.20, 0.08 (each s, each 18H; SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 27°C): δ = 41.4 (br. d, ¹J(C,H) = 111 Hz; (B₂H)BCHSi), 28.8 (d, ¹J(C,H) = 122 Hz; CHSi), 27.2 (br. d, overlapping, B₃BCHSi), 0.6, 0.2, –3.7 (each q; SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27°C): δ = 50, 26.

5b: Yellow solid, m.p. 102°C (decomp), yield 96%; ¹H NMR (300 MHz, C₆D₆, 27°C): δ = 2.40 (d, ³J(H,H) = 3.2 Hz, 2H; B₃BCHSi), 2.37 (d, ³J(H,H) = 2.9 Hz, 2H; (B₂Cl)BCHSi), 1.53 (pseudo triplet, ³J(H,H) = 2.9 Hz, 2H; CHSi), 0.29, 0.22, 0.08 (each s, each 18H; SiMe₃); ¹³C NMR (75 MHz, C₆D₆, 27°C): δ = 48.3 (br. d, ¹J(C,H) = 110 Hz; (B₂Cl)BCHSi), 27.7 (br. d, ¹J(C,H) = 116 Hz; B₃BCHSi), 24.8 (d, ¹J(C,H) = 122 Hz; CHSi), 1.9, 0.3, –3.0 (each q; SiMe₃); ¹¹B NMR (96 MHz, C₆D₆, 27°C): δ = 62, 28.

6a·0.2 4-*tert*-butylpyridine: Yellow solid, m.p. 112°C , yield 85%; ¹H NMR (500 MHz, [D₈]Toluol, -50°C): δ = 8.67 (br. s, 2H; coord. Pyr), 8.59 (s; Pyr), 7.13 (br. s, 1H; BH), 6.74 (s; Pyr), 6.40 (s, 2H; coord. Pyr), 4.45 (br. s, 1H; BH), 2.38 (m, 1H; CHSi), 2.22 (d, 1H; CHSi), 1.92–1.86 (m, 2H; CHSi), 1.84 (d, 1H; CHSi), 1.02 (s; Pyr), 0.83 (s, 9H; coord. Pyr), 0.75 (m, 1H; CHSi), 0.55, 0.53, 0.38, 0.33, –0.06, –0.34 (each s, each 9H; SiMe₃); at 27°C the ¹H NMR spectrum displays one broad signal at 6.28 instead of two broad signals at 7.13 and 4.45.

coordinated" boron triangle B2,B3,B4 the distances shorten by ca. 5 pm upon addition of pyridine.

These unusual properties can be explained by the fact that **5a** and **6a** (just as **1**, **2**, and **3**) are two-electron aromatics. The cyclic delocalization of two π electrons over four boron centers in **5a** and over three boron centers in **6a** is only possible when the axes of the p orbitals of the boron atoms at the corners of the diamond in **5a** or at the noncoordinated corner in **6a** are perpendicular to the plane formed by the boron triangle. For this to occur, the four neighboring atoms of these particular boron atoms must lie in one plane. The addition of one pyridine molecule to **5a** transforms the 4c2e aromatic **5a** into the 3c2e aromatic **6a**, in which the two π electrons are delocalized over the boron triangle without coordinated pyridine. The B...B distances are intermediate between those in the negatively charged prototype **1** and those in the hydrogen-bridged **2** (Scheme 1). The bridging hydrogen bond in **2** corresponds to the BHR...pyridine bridge in **6a**. Addition of a second pyridine molecule to **6a** would result in loss of the cyclic delocalization of the two π electrons and thus in loss of the aromaticity. Density functional calculations^[10] show that the transformation of the 4c aromatic **3** into the 3c aromatic **8** requires about 11 kcal mol⁻¹. In contrast, the transformation of **8** into **9** with loss of aromaticity requires almost 34 kcal mol⁻¹ (Scheme 3).



Scheme 3. Computed^[10] energies required for the transformation of **3** into **8** and of **8** into **9**. In both cases a planar-tetracoordinate boron atom is transformed into a tetrahedrally coordinated one.

The remarkably short B2...B2a distance in **5a** is a result of low ring strain and strong 1,3- π overlap^[15] along the short diagonal. The distortion of a four-membered ring with four 2c2e σ bonds to form a diamond would lead to significant ring strain, owing to smaller angles between two electron pairs. In the four-membered rings described here only four electrons are available for the σ framework to form two B-B-B 3c2e σ bonds, as shown by a natural bond orbital (NBO) analysis for **3**. The bonding 1,3-interaction is further strengthened by a 4c2e π bond, whose electrons according to the NBO analysis are preferentially (36% each) localized on the boron centers of the short diagonal. In contrast, additional σ electrons must

occupy molecular orbitals with 1,3-antibonding character.^[16] This explanation is supported by the fact that the B...B distance in **9** (165.2 pm) with six σ framework electrons is significantly longer than in **8** and **3** (150.9 and 153.0 pm, respectively) with four σ framework electrons each. In addition, the B...B distance of 163.3 pm for the short diagonal in **10**,^[16] which has six electrons available for the σ framework, is similar to that in **9**.

Received: November 2, 2001 [Z18154]

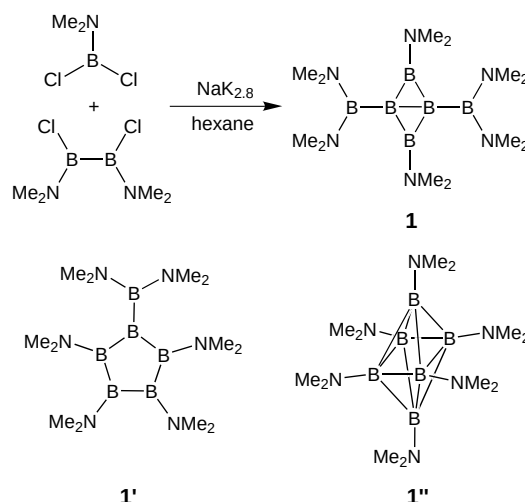
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A Planar, Aromatic *bicyclo*-Tetraborane(4)**

Alexandra Maier, Matthias Hofmann, Hans Pritzkow, and Walter Siebert*

Dedicated to Professor Philipp Gülich

Recently we demonstrated that the dehalogenation of bis(dialkylamino)dichlorodiboranes(4) provides colorful tetraborane(4) derivatives (BR)₄. The blue diisopropylamino derivative displays a folded B₄ ring, whereas a yellow tetrabora-tetrahedrane is formed with the larger 2,2',6,6'-tetramethylpiperidino substituents.^[1] The existence of planar^[2] (BNMe₂)₄ could not be confirmed.^[3] We report here on the *bicyclo*-tetraborane(4) **1**, whose boron atoms form a planar B₄ diamond (Scheme 1).



Scheme 1.

The reaction of a mixture of Me₂NBCl₂ and (Me₂N)₂B₂Cl₂^[4] with NaK_{2.8} alloy in hexane produced neither the anticipated B₃ nor a B₅ ring. Instead a colorless compound of the composition B₆(NMe₂)₆ (EI-MS, *m/z* 330) was formed in addition to oily products of unknown structure. This new compound is a constitutional isomer of the orange *cyclo*-(BNMe₂)₆, a chair-shaped compound that was first obtained in low yields by Nöth and Pommerening^[5] upon dehalogenation of (Me₂N)₂BCl. The colorless B₆(NMe₂)₆ displays three ¹¹B NMR signals at δ = 6, 41, and 63.^[6] The pattern of the signals corresponds to a four-membered ring with two different substituents. The isomers **1'** and **1''** can therefore be excluded.

The crystal-structure analysis^[7] of **1** displays a planar, diamond-shaped B₄ ring. The short distance across the diagonal (1.633(2) Å) indicates the presence of a B–B bond

[*] Prof. Dr. W. Siebert, Dipl.-Chem. A. Maier, Dr. M. Hofmann, Dr. H. Pritzkow
Anorganisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-54-5609
E-mail: ci5@ix.urz.uni-heidelberg.de

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

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(Figure 1). Even shorter transannular B–B bonds (1.524(3) and 1.511(3) Å)^[9] were observed in the diamond-shaped tetraborane(6) **2** and its pyridine adduct (Scheme 2). In **1** the

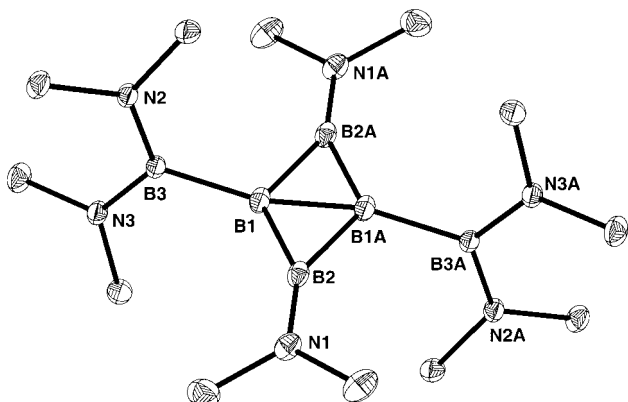
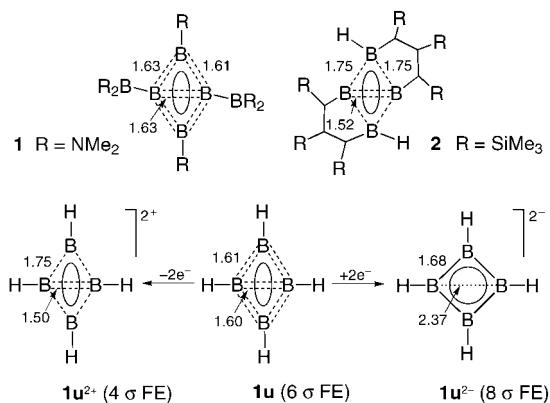


Figure 1. Molecular structure of **1** in the crystal; for reasons of clarity hydrogen atoms are not shown. Selected bond lengths [Å] and angles [°]: B1–B2 1.605(2), B1–B2A 1.632(2), B1–B1A 1.633(2), B1–B3 1.691(2), N1–B2 1.381(2), N2–B3 1.426(1), N3–B3 1.430(1); B1–B2–B1A 60.58(9), B2–B1–B2A 119.42(9), B2–B1–B3 124.05(10), B2A–B1–B3 114.45(9).



Scheme 2.

sides of the diamond that are opposite to each other have the same length (1.605(2) and 1.632(2) Å). Remarkably, atoms B3 and B3A of the exocyclic (Me₂N)₂B substituents lie slightly above and below the B₄ plane (0.4 Å), and the planes N2,B3,N3 and N2A,B3A,N3A are nearly perpendicular (78.9°) to the B₄ ring. The N1,C1,C2 plane forms an angle of 11.4° with the plane of the ring. The B–N bond lengths at B2 and B2A (1.381(2) Å) indicate a π interaction between the boron and nitrogen atoms, whereas the B–N bonds of the (Me₂N)₂B substituents are significantly longer (1.430(1) Å). Since atoms B1 and B1A each have connectivities to four boron atoms, and as there are only eight electrons available for the formation of five “bonds” in the B₄ diamond, a nonclassical bonding situation must be present.

A density functional calculation was carried out to explain the electronic structure of **1**.^[10] In the case of the B₄H₄ parent compound, a D_{4h} -symmet-

ric cycle with classical bonding (Figure 2) does not represent the minimum on the potential energy hypersurface. In fact, it is 65 kcal mol^{−1} higher in energy than the tetrahedrane isomer (*T_d*, minimum).^[11] A more stable structure results when in *cyclo*-(BH)₄ the π molecular orbital (π -MO; b_{3u}) made up of four p_z atomic orbitals is occupied with an electron pair (Figure 2) that formally originates from one of the four σ MOs of the B₄ framework. Jahn–Teller distortion lowers the symmetry from D_{4h} to D_{2h} , whereby one of the originally degenerate MOs (e_u) is raised in energy (b_{2u}) but remains unoccupied (Figure 2). In exchange, the second MO (b_{1u}), along with the π MO, is strongly stabilized as a result of favorable 1,3-interactions between B1 and B1A. The third σ MO (b_{3g}) is only slightly higher in energy than in the D_{4h} -symmetric structure and now forms the HOMO. The structure with D_{2h} symmetry is 81 kcal mol^{−1} more stable than that with D_{4h} symmetry.

The geometric distortion is accompanied by a rehybridization at B2 and B2A from sp^2 to sp . For these two atoms the increase in the s fraction in the occupied MOs results in a high p character for the unoccupied σ MO, which acts as the acceptor level for the *exo*- σ bonds with B1 and B1A. In the case of B₄H₄ this hyperconjugation interaction leads to the formation of a 3c2e B–H–B bridge.^[11] However, in the presence of less effective σ donors there is only a shift of the terminal substituents at B1 and B1A in the molecular plane towards B2 and B2A (Table 1). The deviation of the B₆ framework from planarity observed in **1** cannot be due to crystal packing and steric effects, since calculations predict a nonplanar structure for **1** as well as for model compounds with less sterically bulky substituents. Based on the results presented in Table 1 the amino substituents at B2 and B2A seem to be responsible for the nonplanar structure.

The variations between the frameworks of **1** and **2** result from the differences in the number of framework electrons (FEs). In **1** there are eight FEs ($6\sigma + 2\pi$), but only six are available in **2** since two are required for bonding the two additional H atoms (Scheme 2). These six electrons form two

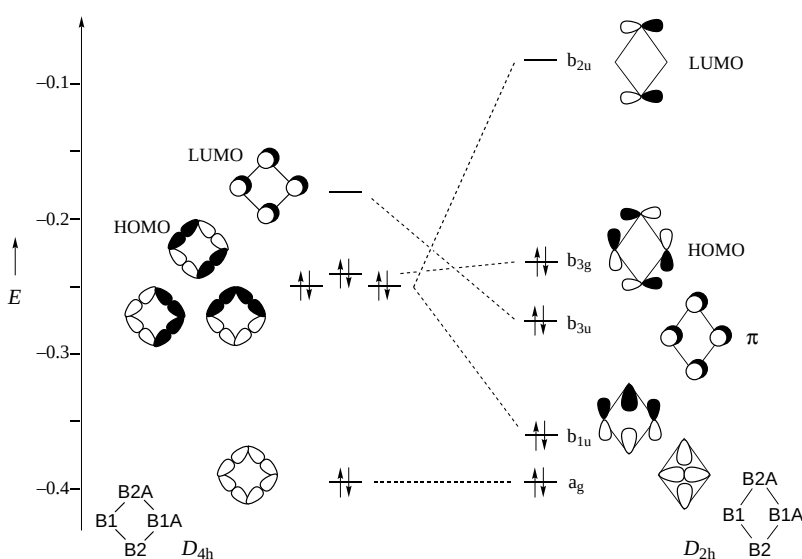
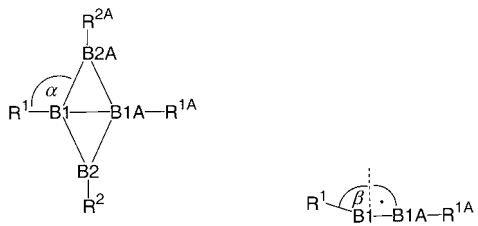


Figure 2. Molecular orbitals relevant for the bonding of the B₄ unit in B₄H₄ with D_{4h} and D_{2h} symmetry.

Table 1. Angles α and β as a measure of the distortion of *bicyclo-tetraboranes*(4) with two different substituents.



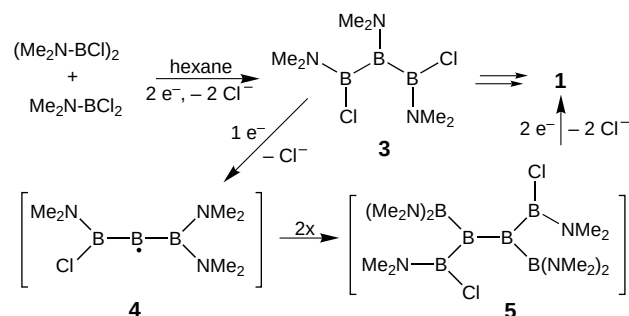
R ¹ , R ^{1A}	R ² , R ^{2A}	α	β
H	H	73.4	90.0
BH ₂	H	87.2	90.0
B(NH ₂) ₂	H	94.4	90.0
H	NH ₂	100.3	52.9
BH ₂	NH ₂	91.8	73.6
B(NH ₂) ₂	NH ₂	95.2	74.7
B(NMe ₂) ₂	NMe ₂	113.2	70.4
B(NMe ₂) ₂ ^[a]	NMe ₂ ^[a]	114.4 ^[a]	75.7 ^[a]

[a] Experimental results.

3c2e σ bonds (triangles drawn with dashed lines) and one four-center π bond (ellipsoid). Furthermore in **1** there is a 4c2e π bond. In addition to two 3c2e σ bonds (represented in Figure 2 by the a_g and b_{1u} MOs and in Scheme 2 by two triangles with dashed lines) a further σ MO (b_{3g}) is occupied that shows bonding character along the edges (1.61, 1.63 Å in **1** compared to 1.75 Å in **2**) but antibonding character with regard to the shorter diagonals (1.63 Å compared to 1.52 Å in **2**; diamond drawn with dashed lines). The σ bonding in **1** is therefore intermediate to that in **2** and a classical B₄ ring in which eight electrons form four 2c2e σ bonds. The description of the bonding situation and the relationship between **1** and **2** is supported by calculations^[12] on **1u**²⁺, whose edges (1.75 Å) and short diagonal (1.50 Å) correspond to those of **2**. The results for **1u** (edge length 1.61 Å, diagonal length 1.60 Å) also fit the values for **1**. In the case of **1u**²⁻ edge lengths of 1.68 Å and a diagonal length of 2.37 Å were calculated.

McKee reported that a D_{3d} -symmetric B₆ ring is the most stable B₆(NH₂)₆ isomer, but in his calculations he did not consider the isomer derived from **1**.^[13] Our calculations show that this isomer is 10.3 kcal mol⁻¹ lower in energy than the D_{3d} -symmetric structure. However, the relative stabilities are reversed in the case of Me₂N-substituted derivatives: The D_{3d} -symmetric B₆(NMe₂)₆ ring is 8.0 kcal mol⁻¹ more stable than **1** (C_i).

For the formation^[14] of **1** we suggest the reaction mechanism shown in Scheme 3, which is supported by recent results



Scheme 3. Proposed mechanism for the formation of **1**.

from Berndt et al. (the synthesis of **1** in 40–50 % yield by the reaction of **3**^[15] with Na/K alloy in pentane or with lithium naphthalenide in THF).^[9] It is proposed that dehalogenation of the reagents in hexane provides the triborane **3**, and subsequent chloride elimination and Me₂N migration lead to the radical **4**. After dimerization of **4** to **5** renewed chloride elimination could result in cyclization to form **1**.

Experimental Section

1: NaK_{2.8} alloy (2 mL) was placed in hexane (100 mL). Then a mixture of 1,2-dichloro-1,2-bis(dimethylamino)diborane(4) (4.17 g, 23 mmol) and dichlorodimethylaminoborane (2.90 g, 23 mmol) was slowly added. The reaction mixture was stirred at room temperature for 6 days and then filtered, and the brown filtrate was concentrated. Compound **1** (20 mg, 0.5 %; m.p. 105 °C) crystallized from a solution of the oily crude product (2.3 g) in hexane at –80 °C.

¹¹B NMR (C₆D₆, 96 MHz): δ = 6 (linewidth 330 Hz), 41 (350 Hz), 63 (350 Hz); HR-EI-MS m/z calcd for ¹²C₁₂¹H₃₆¹¹B₆¹⁴N₆: 330.3560, found: 330.3516.

Received: November 5, 2001 [Z18159]

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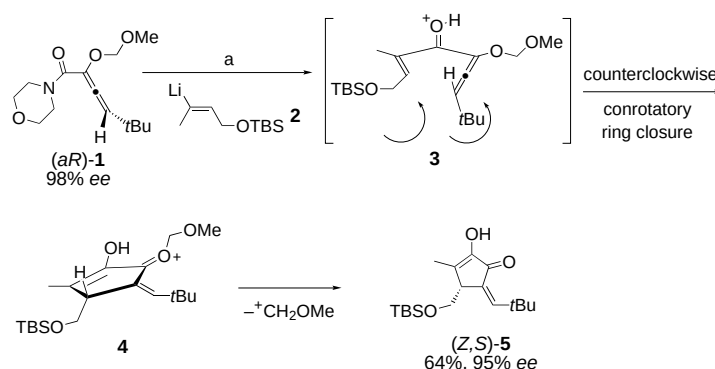
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Synthesis of Enantioenriched 5-Alkylidene-2-cyclopentenones from Chiral Allenyl Carbamates: Generation of a Chiral Lithium Allenolate and Allylic Activation for a Conrotatory 4π -Electrocyclization**

Carsten Schultz-Fademrecht, Marc A. Tius,*
Stefan Grimme,* B. Wibbeling, and Dieter Hoppe*

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

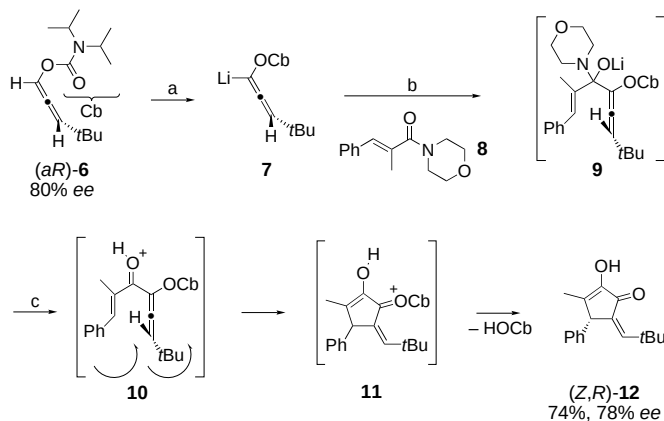
Chiral allenes have assumed an increasing importance in organic synthesis.^[1, 2] A surprising application was reported by Tius et al.^[3] Allenyl alkenyl ketone (*aR*)-**3** cyclized under proton catalysis to form optically active 5-((*Z*)-alkylidene)-2-hydroxy-2-cyclopentenone **5** (Scheme 1). The chirality of the axial unit was transferred to the tetrahedral carbon atom of the cyclopentenone by means of a conrotatory electrocyclization of the 4π -system **3**, in a process that is similar to the



Scheme 1. Cyclization of (*aR*)-**1**. a) **2**, THF, -78°C , 30 min; 2) saturated aqueous KH_2PO_4 . TBS = *tert*-butyldimethylsilyl.

Nazarov reaction.^[4] The cyclization occurs through a counter-clockwise conrotation because of steric demands.^[5]

Hoppe and co-workers had developed a simple method for the synthesis of enantiomerically enriched allenyl carbamate **6** (Scheme 2),^[6] which initiated a collaboration to utilize **6** in this modified Nazarov reaction. Herein we describe a new stereospecific ring closure, which can be seen as a hybrid of an intramolecular vinylic cycloalkylation of a lithium allenolate and a modified Nazarov cyclization. The lithiation of allene (*aR*)-**6** (80% *ee*)^[6] and subsequent acylation with (*E*)-alkenoylmorpholinide **8**, followed by transfer of the reaction mixture into hydrochloric acid in ethanol (5%), occurred as expected for the modified Nazarov cyclization to give hydroxycyclopentenone (*Z,R*)-**12**^[7] (Scheme 2, 74%, 78% *ee*). The chirality transfer amounted to 98%.



Scheme 2. Cyclization of (*aR*)-**6**. a) *n*BuLi, TMEDA, toluene, -78°C , 30 min; b) **8**, -78°C , 2.5 h; c) rapid transfer of the mixture through a cannula into a solution of HCl in ethanol (5%). TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

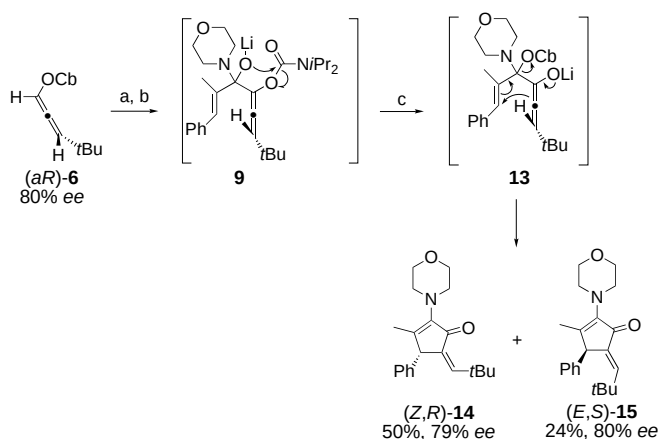
When the reaction mixture was warmed to room temperature after the addition of amide **8** to the lithiated allenyl carbamate **7**, diastereomers of 2-morpholine-2-cyclopentenone (*Z,R*)-**14** and (*E,S*)-**15** were isolated in 74% yield, with >98% chirality transfer (Scheme 3). We assume that a rearrangement of intermediate **9**, which involves a migration of the *N,N*-diisopropylcarbamoyl group (Cb), leads to the formation of a lithium 1,2-dienolate (an “allenolate”).^[8, 9] The

[*] Prof. Dr. S. Grimme, Prof. Dr. D. Hoppe, Dr. C. Schultz-Fademrecht, B. Wibbeling
Organisch-chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36531
E-mail: grimmes@uni-muenster.de
dhoppe@uni-muenster.de

Prof. Dr. M. A. Tius
Department of Chemistry, University of Hawaii at Manoa
2545 The Mall, Honolulu, HI 96822-2275 (USA)
Fax: (+1) 808-956-5908
E-mail: tius@gold.chem.hawaii.edu

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 424), the Fonds der Chemischen Industrie and the Alexander von Humboldt Foundation. M.A.T. thanks the National Institutes of Health (GM57873) for generous support. We thank K. Gottschalk for her skillful technical assistance.

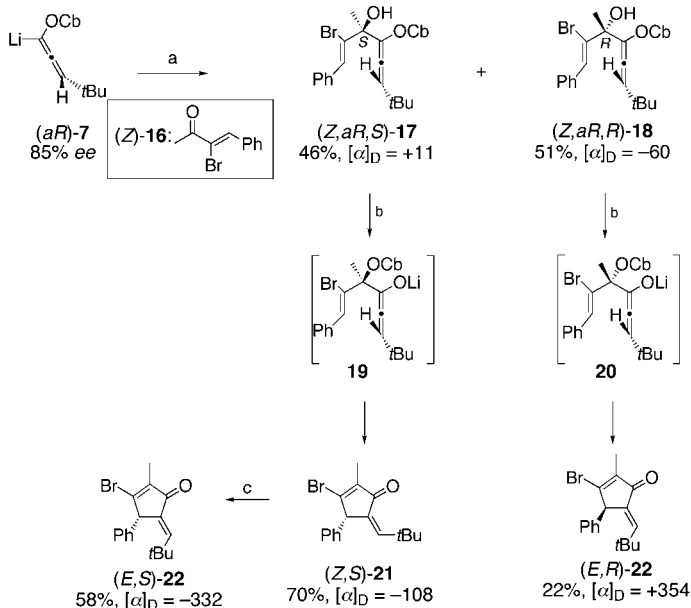
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Scheme 3. Cyclization to **14** and **15**. a) *n*BuLi, toluene, -78°C , 30 min; b) **8**, 1 h; -78°C ; c) 1) 1 h, room temperature; 2) HCl (2N). Cb = CO- NiPr_2 .

bisallylic tertiary carbamoyloxy group acts as a leaving group during the cycloalkylation; which leads to (Z,R)-**14** and (E,S)-**15**.

The different geometries of the exocyclic double bonds in diastereomers **14** and **15** and the very high chirality transfer suggests a conrotatory mechanism for the modified Nazarov cyclization, but also raises a question: is the direction of the conrotation controlled by the steric requirement of the allene, or does the new stereocenter at C4 in **13** determine the stereochemistry? We were able to determine the absolute configuration of the intermediates and the products of the reaction of (aR)-**7** and (Z)- α -bromo enone **16**^[10] (Scheme 4). The epimeric adducts (Z,aR,S)-**17** and (Z,aR,R)-**18** were synthesized by hydrolyzing the intermediate lithium alkoxides at low temperature and separating by flash column

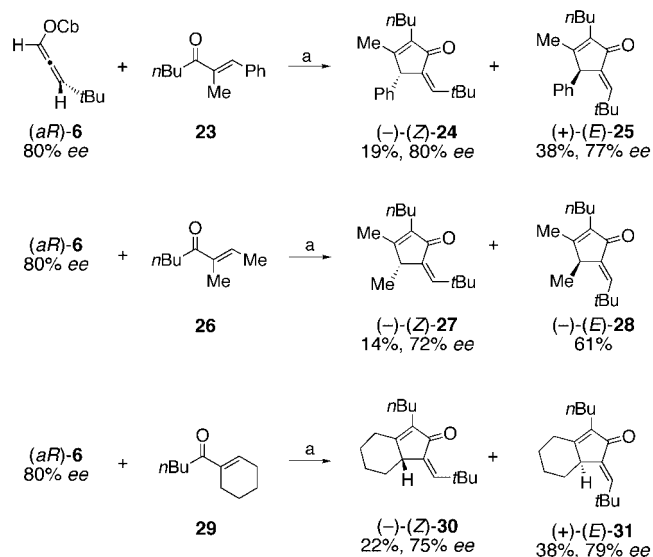


Scheme 4. Independent cyclization of **17** and **18**. a) 1) *n*BuLi, toluene, -78°C , 30 min; 2) **16**, 10 min, -78°C ; 3) saturated aqueous NH_4Cl ; b) 1) *n*BuLi, TMEDA, toluene, 1 h, -78°C , 1 h, room temperature; 2) HCl (2N); c) benzene, room temperature, 48 h.

chromatography. Because crystalline derivatives of these sensitive tertiary alcohols could not be prepared, we determined the absolute configuration of epimer **17** by time-dependent density functional response theory (TDDFT).^[11]

Both alcohols (Z,aR,S)-**17** and (Z,aR,R)-**18** were deprotonated separately with *n*BuLi/TMEDA in toluene. Subsequent warming of the reaction mixture to room temperature led to the isolation of cyclopentenones (Z,S)-**21** (70%, $[\alpha]_D^{20} = -108$) and (E,R)-**22** (22%, $[\alpha]_D^{20} = +354$), respectively, with no traces of the other isomer. The absolute configuration of (E,R)-**22** was elucidated by X-ray crystallographic analysis.^[12a] Exposure of (Z,S)-**21** ($[\alpha]_D^{20} = -108$) to daylight led to (E,S)-**22** ($[\alpha]_D^{20} = -332$), the enantiomer of the (E,R)-**22**.

The topology of the ring closure is determined by the stereochemistry of the carbon that bears the leaving group. In the cycloalkylation (as in the modified Nazarov cyclization) a conrotatory ring closure takes place in a manner that is an allowed *anti* S_{E}' substitution in the allylic system. Apparently the cleavage of the C-OCb bond in the transition state has progressed to the stage that the developing partial positive charge is sufficient to follow the stereoelectronic requirements of 4π cyclizations.^[13] Further examples of this reaction in which the intermediate epimeric alcohols were not isolated are shown in Scheme 5.^[7]



Scheme 5. Cyclization reactions with different enones. a) 1) *n*BuLi, toluene, -78°C , 30 min; 2) enone **23**, **26**, or **29**, 1 h, -78°C , then 1 h, room temperature; 3) HCl (2N).

In conclusion, we have reported an unusual method for the conversion of chiral allenyl carbamates into highly substituted 5-alkylidene-2-cyclopentenones. The process is characterized by:

- a stereoretentive α -lithiation and subsequent carbonyl addition of an allenyl carbamate;
- a simultaneous activation of nucleophilic and electrophilic characteristics of the open-chain intermediate by the migration of the carbamoyl group; and
- a stereospecific conrotatory ring closure of the 4π -electron system.

Experimental Section

Reactions were performed under an argon atmosphere in flame-dried glassware. *n*BuLi (1.3 equiv, 1.6 M in hexane) was added to a solution of (*aR*)-**6** (1.5 equiv) and TMEDA (1.5 equiv) in absolute toluene (6 mL mmol⁻¹) at -78 °C. After 30 min, a solution of an enone or an unsaturated amide (1.0 equiv) in absolute toluene (2 mL mmol⁻¹) at -78 °C was added through a cannula. The reaction mixture was stirred for 1 h at -78 °C and for 1 h at room temperature. The mixture was then quenched by the rapid addition of HCl (1 N, 10–20 mL mmol⁻¹) and diethyl ether (10–20 mL mmol⁻¹) and stirred for 3 min. After the aqueous layer was extracted three times with diethyl ether, the combined organic layers were neutralized with NaHCO₃, dried over Na₂SO₄, and concentrated under vacuum. Purification by flash column chromatography gave the desired cyclopentenone. (Spectroscopic data can be found in the Supporting Information.)

Received: November 19, 2001 [Z18243]

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performed within the framework of time-dependent density functional theory (TDDFT),^[11f] as is described in ref. [11g]. In these calculations, diffuse functions (C, O, N, Br: [1s1p1d], H: [1s1p]) were added to the SV(P) basis and the B3LYP hybrid functional^[11h] was employed. We calculated an optical rotation of $[\alpha]_D = +64$ for (*Z,aR,S*)-**17** and $[\alpha]_D = -50$ for (*Z,aR,R*)-**18**, which allows a definite assignment of the absolute configuration. The almost opposite $[\alpha]_D$ values of these diastereomers shows that the bromostyrene chromophore has the greatest influence on the optical rotation. To prove these results, we calculated (at the same level of theory) the $[\alpha]_D$ values of two conformations (nonplanar bromostyrene substituent) of the *E* isomer (*E,aR,R*)-*N,N*-diisopropylcarbamidic acid 1-(2-bromo-1-hydroxy-1-methyl-3-phenylpropenyl)-4,4-dimethyl-1,2-butadienyl ester (**32**), for which the absolute configuration was determined by X-ray crystal-structure analysis under anomalous X-ray dispersion conditions.^[12b] The results of these calculations are in perfect agreement with the experimental data. b) TURBOMOLE (Vers. 5.3): R. Ahlrichs, M. Bär, H.-P. Baron, R. Bauernschmitt, S. Böcker, M. Ehrig, K. Eichkorn, S. Elliott, F. Furche, F. Haase, M. Häser, H. Horn, C. Huber, U. Huniar, M. Kattannek, C. Kölmel, M. Kollwitz, K. May, C. Ochsenfeld, H. Öhm, A. Schäfer, U. Schneider, O. Treutler, M. von Arnim, F. Weigend, P. Weis, H. Weiss, Universität Karlsruhe, **2000**; c) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100; J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 8822–8824; d) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571–2577; e) K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Lett.* **1995**, *240*, 283–290; f) R. Bauernschmitt, R. Ahlrichs, *Chem. Phys. Lett.* **1996**, *256*, 454–464; g) S. Grimme, *Chem. Phys. Lett.* **2001**, *339*, 380–388; P. J. Stephens, F. J. Devlin, J. R. Cheeseman, M. J. Frisch, *J. Phys. Chem. A* **2001**, *105*, 5356–5371; h) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

- [12] a) X-ray crystal-structure analysis of **22**: C₁₇H₁₉OBr, *M*_r = 319.23, orthorhombic, space group *P*2₁2₁ (no. 19), *a* = 6.469(1), *b* = 13.857(1), *c* = 17.202(4) Å, *V* = 1542.0(3) Å³, ρ_{calcd} = 1.375 g cm⁻³, colorless crystal, 0.25 × 0.20 × 0.15 mm, μ = 35.39 cm⁻¹, empirical absorption correction by means of ψ scan data (0.472 ≤ *T* ≤ 0.619), *Z* = 4, λ = 1.54178 Å, *T* = 223 K, $\omega/2\theta$ scans, 1818 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.62$ Å⁻¹, 1818 independent and 1734 observed reflections with $[I \geq 2\sigma(I)]$, 177 refined parameters, *R* = 0.028, *wR*² = 0.081, max. residual electron density = 0.27 (–0.25) e Å⁻³, Flack parameter 0.04(3), hydrogen atoms calculated and refined as riding atoms; b) X-ray crystal structure analysis of **32**: C₂₄H₃₄NO₃Br, *M*_r = 464.43, monoclinic, space group *P*2₁/*n* (No. 14), *a* = 9.668(1), *b* = 12.688(1), *c* = 20.590(1) Å, β = 97.90(1)°, *V* = 2501.8(3) Å³, ρ_{calcd} = 1.233 g cm⁻³, colorless crystal, 0.35 × 0.20 × 0.20 mm, μ = 16.65 cm⁻¹, empirical absorption correction by means of SORTAV (0.593 ≤ *T* ≤ 0.732), *Z* = 4, λ = 0.71073 Å, *T* = 198 K, ω and ϕ scans, 16314 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.65$ Å⁻¹, 5948 independent (*R*_{int} = 0.040) and 3996 observed reflections $[I \geq 2\sigma(I)]$, 271 refined parameters, *R* = 0.039, *wR*² = 0.078, max. residual electron density = 0.22 (–0.42) e Å⁻³, hydrogen atoms calculated and refined as riding atoms. The data sets were collected with an Enraf–Nonius CAD4 and a Nonius Kappa CCD diffractometer, the later equipped with a rotating anode generator Nonius FR591. Programs used: data collection: EXPRESS (Nonius B.V., **1994**) and COLLECT (Nonius B.V., **1998**), data reduction MoLEN (K. Fair, Enraf–Nonius B.V., **1990**) and Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction for CCD data SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–37; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics SCHAKAL (E. Keller, Universität Freiburg, **1997**). CCDC-173069 and -173919 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
- [13] A related reaction mechanism is the electrocyclic ring opening of cyclopropyl tosylates; the direction of the ring opening depends on the stereochemistry of the carbon atom that bears the leaving group:

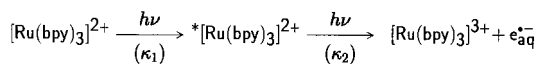
a) J. D. Roberts, V. C. Chambers, *J. Am. Chem. Soc.* **1951**, 73, 5034–5040; b) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, 87, 395–397; c) H. C. Longuet-Higgins, W. H. Abrahamson, *J. Am. Chem. Soc.* **1965**, 87, 2045–2048; d) W. Kutzelnigg, *Tetrahedron Lett.* **1967**, 4965–4971; e) U. Schöllkopf, *Angew. Chem.* **1968**, 80, 603–613; *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 588–598; f) P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, J. Paust, K. Fellnerberger, *J. Am. Chem. Soc.* **1972**, 94, 125–133.

Near-UV Photoionization of $[\text{Ru}(\text{bpy})_3]^{2+}$: A Catalytic Cycle with an Excited Species as Catalyst**

Martin Goetz,* Martin Schiewek, and Mohammad H. O. Musa

Photoionization of the tris-2,2'-bipyridyl ruthenium(II) ion $[\text{Ru}(\text{bpy})_3]^{2+}$ is the archetype of a class of reactions that might effect photochemical water splitting:[1] the ejected electron e_{aq}^- reacts with H^+ , ultimately yielding hydrogen,[2] and the remaining oxidized complex $[\text{Ru}(\text{bpy})_3]^{3+}$ is thermodynamically capable of oxidizing OH^- to oxygen,[1] although in practice this has only been realized with additional cocatalysts[3] or in microheterogeneous environments.[4] Herein, we identify the excited metal-to-ligand charge-transfer (MLCT) complex $^*[\text{Ru}(\text{bpy})_3]^{2+}$ as a catalytic intermediate of this photoionization. Near-UV light (308 or 355 nm) drives both the ionization of this species and the reduction of $[\text{Ru}(\text{bpy})_3]^{3+}$, which then regenerates the ruthenium(II) complex in its excited state.

Despite its model character, the mechanism of photoionization in this system has received very little attention. On the basis of flash-lamp experiments with polychromatic light (300–360 nm, 17 μs flash duration) and indirect detection of e_{aq}^- , a sequential reaction (Scheme 1) with a very low quantum yield of the ionization proper (0.0015) was proposed.[5a] Later studies using nanosecond laser flash photolysis, with optical detection of e_{aq}^- , gave somewhat contradictory results for the dependence of the electron yield on the excitation intensity,[5b, c] and focused mainly or exclusively[5d] on the effect of surface-active molecules on the electron yield.



Scheme 1. Linear reaction sequence for photoionization of $[\text{Ru}(\text{bpy})_3]^{2+}$.

[*] Prof. Dr. M. Goetz, M. Schiewek, M. H. O. Musa
Fachbereich Chemie
Martin-Luther-Universität Halle-Wittenberg
Kurt-Mothes-Strasse 2, 06120 Halle/Saale (Germany)
Fax: (+49) 345-55-27657
E-mail: goetz@chemie.uni-halle.de

[**] This work was supported by the Volkswagen Foundation. We are grateful to a referee for suggesting the scavenging experiment with benzoic acid; bpy = 2,2'-bipyridine.

To elucidate the mechanism and determine the relevant photokinetic parameters, we decided to investigate the intensity dependence of the yield not only for the final product e_{aq}^- but also for the presumed intermediate $^*[\text{Ru}(\text{bpy})_3]^{2+}$. Such an approach obviously provides much more information about a reaction that is expected to have multiple steps. Laser flash photolysis with different excitation wavelengths and detection of luminescence or optical absorbance was performed (see Experimental Section).

Figure 1a shows the dependence of the concentrations of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ and e_{aq}^- , relative to the starting concentration c_0 of $[\text{Ru}(\text{bpy})_3]^{2+}$, on the excitation intensity at 308 nm. A high turnover can be achieved; at our highest laser intensity the electron concentration approaches 50 % of c_0 .

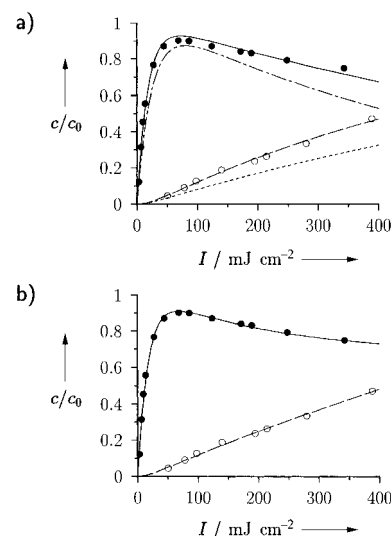


Figure 1. Photoionization of $3 \times 10^{-5} \text{ M } [\text{Ru}(\text{bpy})_3]^{2+}$ with light of wavelength 308 nm. The concentrations c , relative to the substrate concentration c_0 , of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ (●) and e_{aq}^- (○) are shown as functions of the laser intensity I . a) The fit curves refer to the mechanism of Scheme 1: — shows a fit of Equation (1) to the experimental data for $^*[\text{Ru}(\text{bpy})_3]^{2+}$, which yields the best-fit parameters $\kappa_1' = 5.68 \times 10^{-2} \text{ cm}^2 \text{ mJ}^{-1}$, $\kappa_2' = 1.03 \times 10^{-3} \text{ cm}^2 \text{ mJ}^{-1}$, --- the curve calculated with κ_1' and κ_2' for e_{aq}^- [Eq. (2)]. --- is the best fit of Equation (2) to the experimental data for e_{aq}^- , yielding $\kappa_1'' = 4.21 \times 10^{-2} \text{ cm}^2 \text{ mJ}^{-1}$, and $\kappa_2'' = 1.69 \times 10^{-3} \text{ cm}^2 \text{ mJ}^{-1}$, and ●— is the calculated result with κ_1'' and κ_2'' for $^*[\text{Ru}(\text{bpy})_3]^{2+}$ [Eq. (1)]. b) The curves refer to the mechanism of Scheme 2, and are simultaneous fits of Equation (3) to the experimental data for $^*[\text{Ru}(\text{bpy})_3]^{2+}$ (—) and of Equation (4) to those for e_{aq}^- (---). Best-fit parameters are $\kappa_1 = 5.73 \times 10^{-2} \text{ cm}^2 \text{ mJ}^{-1}$, $\kappa_2 = 1.52 \times 10^{-3} \text{ cm}^2 \text{ mJ}^{-1}$, and $\kappa_3 = 3.19 \times 10^{-3} \text{ cm}^2 \text{ mJ}^{-1}$.

Because the concentrations of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ and e_{aq}^- are measured immediately after the end of the 308 nm pulse, the whole reaction sequence leading to photoionization must be completed within about 25 ns. On that time scale, bimolecular steps involving two ruthenium-based species, or one such species and e_{aq}^- , are negligible at the low concentrations used. As our solutions were optically thin, all the absorption steps can be described as first-order processes.[6] For a simple two-step photoreaction according to Scheme 1, that is, for the mechanism proposed in the literature, the intensity dependences of the observed species would be given by Equations (1) and (2). These expressions are valid for random shapes of the laser pulse, and depend only on its total intensity I

$$\frac{*[Ru(bpy)_3]^{2+}}{c_0} = \frac{\kappa_1}{\kappa_1 - \kappa_2} (e^{-\kappa_2 I} - e^{-\kappa_1 I}) \quad (1)$$

$$\frac{e_{aq}^-}{c_0} = 1 - \frac{\kappa_1 e^{-\kappa_2 I} - \kappa_2 e^{-\kappa_1 I}}{\kappa_1 - \kappa_2} \quad (2)$$

(see ref. [6]). The constants κ_1 and κ_2 correspond to the rate constants in formal kinetics but have a reciprocal-intensity dimension ($\text{cm}^2 \text{mJ}^{-1}$ in our case).

However, attempts to fit the two Equations (1) and (2) to the data reveal that the kinetic model in Scheme 1 must be wrong, or at least incomplete. While acceptable fits can be obtained for each species alone (by fitting Equation (1) to the intensity dependence of the triplet concentration, and independently fitting Equation 2 to that of the intensity dependence of the electron concentration), the curves calculated from the resulting best-fit parameters κ_1 and κ_2 for the respective other species strongly deviate from the experimental data, as seen in Figure 1a. Any explanation must account for the fact that with increasing intensity (I), the electron concentration increases almost twice as much as the triplet concentration decreases.

Photoionization of the starting material by a parallel route that bypasses the triplet state is highly unlikely because, on excitation of $[Ru(bpy)_3]^{2+}$, the triplet state forms within 300 fs^[7], with a quantum yield of one.^[8, 9b] Because of the very high redox potential of the Ru^{III}/Ru^{IV} couple,^[10] all routes leading to $[Ru(bpy)_3]^{4+}$ must be discounted for thermodynamic reasons; this includes subsequent monophotonic or biphotonic ionization of $[Ru(bpy)_3]^{3+}$, formed by the pathway in Scheme 1, as well as the ejection of two electrons from a higher excited state of the starting material, in a parallel reaction.

The only remaining possibility is regeneration of the substrate or its triplet-excited form from $[Ru(bpy)_3]^{3+}$, the by-product of photoionization of the triplet species. This reaction is exergonic even for ground-state $[Ru(bpy)_3]^{3+}$, but much too slow to account for the observed effect.^[3] However, irradiation of $[Ru(bpy)_3]^{3+}$ at 660 nm was reported to lead to an increased rate.^[3] As the 308 nm pulse carries more than twice the energy per photon, it seemed conceivable that it might induce a much faster photoreaction. This hypothesis was verified by two-pulse experiments on the oxidized complex $[Ru(bpy)_3]^{3+}$ (Figure 2).

A 532 nm laser pulse provides a convenient analytical tool that is only sensitive to $[Ru(bpy)_3]^{2+}$: it converts $[Ru(bpy)_3]^{2+}$ into its MLCT triplet species $*[Ru(bpy)_3]^{2+}$, which is detected by its characteristic luminescence. However, it does not produce any luminescence from $[Ru(bpy)_3]^{3+}$ at all, nor does it lead to any chemical change of this compound.

Confirmation of the photoinduced transformation of $[Ru(bpy)_3]^{3+}$ into $*[Ru(bpy)_3]^{2+}$ or $[Ru(bpy)_3]^{2+}$ was given by use of a 532 nm pulse followed by a 308 nm pulse (top trace in Figure 2). After the first pulse, no luminescence was detectable, which shows that, initially, our solution of $[Ru(bpy)_3]^{3+}$ did not contain any $[Ru(bpy)_3]^{2+}$. The second pulse gave an intense luminescence of $*[Ru(bpy)_3]^{2+}$, which must have been formed either directly from $[Ru(bpy)_3]^{3+}$ or by conversion of $[Ru(bpy)_3]^{3+}$ into $[Ru(bpy)_3]^{2+}$, and subsequent excitation of the latter species by the same pulse. When

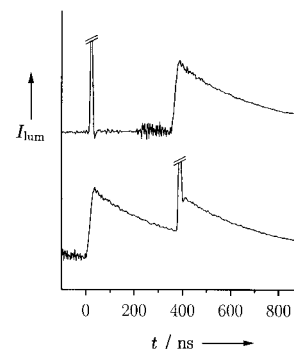


Figure 2. Two-pulse experiments on $3 \times 10^{-5} \text{ M } [Ru(bpy)_3]^{3+}$ at pH 0. The uncalibrated luminescence intensities I_{lum} are displayed as functions of the time t . Top trace: 532 nm pulse (540 mJ cm^{-2}) followed by 308 nm pulse (340 mJ cm^{-2}); bottom trace: sequence reversed. The spikes caused by unsuppressed stray light from the 532 nm pulses have been cut off.

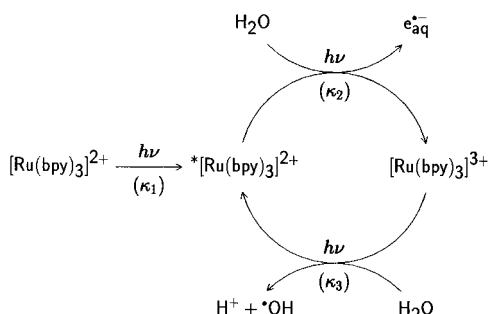
we reversed the sequence of the two pulses in a second experiment (bottom trace in Figure 2), the initial 308 nm pulse produced the expected luminescence, but the subsequent 532 nm pulse also did so, which provides additional confirmation of the formation of a ruthenium(II) species by 308 nm light, rather than an unknown emissive ruthenium(III) species.

A criterion allowing a distinction in this photoreaction between direct formation of $*[Ru(bpy)_3]^{2+}$ from $[Ru(bpy)_3]^{3+}$, and indirect formation (that is, via ground state $[Ru(bpy)_3]^{2+}$ as an intermediate) is provided by the initial slope in a plot of the luminescence as a function of the intensity of the 308 nm pulse. In the case of direct formation of $*[Ru(bpy)_3]^{2+}$, this initial slope must be nonzero, whereas in the case of indirect formation an induction period would result. Our experiments provide good evidence for the former, so 308 nm photolysis of $[Ru(bpy)_3]^{3+}$ produces an electronically excited ruthenium(II) complex.

The mechanism of thermal reduction of $[Ru(bpy)_3]^{3+}$ to $[Ru(bpy)_3]^{2+}$ is complex, and involves more than one molecule of $[Ru(bpy)_3]^{3+}$.^[3, 4] In contrast, the photoinduced reduction observed in this work must be much simpler: because it is fast on the time scale of our laser pulses, it cannot comprise bimolecular steps with species other than water; the situation is thus comparable to that of isolated reactant molecules, for example, in a microheterogeneous environment. When the interactions between $[Ru(bpy)_3]^{3+}$ molecules were suppressed in zeolite cages, $\cdot OH$ radicals were detected in the thermal reduction,^[4] while they were never reported in the homogeneous phase. The formation of radicals in our photoinduced reduction of $[Ru(bpy)_3]^{3+}$, but not in the homogeneous thermal reduction, was confirmed by scavenging experiments with benzoic acid. Benzoic acid is converted by $\cdot OH$ radicals into salicylic acid,^[2] which can be monitored by the fluorescence of the salicylate anion at a pH higher than 4. When a $6 \times 10^{-5} \text{ M}$ solution (stable at pH 0) of $[Ru(bpy)_3]^{3+}$ that contained $5 \times 10^{-3} \text{ M}$ of benzoic acid was made basic with NaOH, the thermal reduction occurred instantaneously, but only an insignificant background signal arising from salicylic acid was recorded in the fluorescence spectrometer. When, however, the same solution was irradiated *before* adding the base with a few laser flashes at 308 nm, such that the UV

spectrum indicated complete conversion into $[\text{Ru}(\text{bpy})_3]^{2+}$, a substantial fluorescence signal of the salicylate anion was detected, which was comparable to the luminescence signal of the regenerated ruthenium(II) species.

The overall photoionization mechanism of $[\text{Ru}(\text{bpy})_3]^{2+}$ is thus cyclic, with $^*[\text{Ru}(\text{bpy})_3]^{2+}$ acting as a catalyst (Scheme 2); this mechanism is also in perfect accordance with the



Scheme 2. Cyclic-photoionization mechanism of $[\text{Ru}(\text{bpy})_3]^{2+}$.

experimental results (Figure 1). Because all three steps of this mechanism are photoreactions that are driven by the same laser pulse, the pulse shape does not play any role in the intensity dependences, and the total intensity I is the only variable determining the concentrations of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ and e_{aq}^- after the pulse. The results are given in Equations (3) and (4).

$$\frac{^*[\text{Ru}(\text{bpy})_3]^{2+}}{c_0} = \frac{\kappa_3}{\kappa_2 + \kappa_3} - \frac{(\kappa_1 - \kappa_3)e^{-\kappa_1 I}}{\kappa_1 - \kappa_2 - \kappa_3} + \frac{\kappa_1 \kappa_2 e^{-(\kappa_2 + \kappa_3)I}}{(\kappa_2 + \kappa_3)(\kappa_1 - \kappa_2 - \kappa_3)} \quad (3)$$

$$\frac{e_{\text{aq}}^-}{c_0} = \frac{\kappa_2}{\kappa_2 + \kappa_3} \left[\left(\frac{\kappa_2}{\kappa_2 + \kappa_3} - \frac{\kappa_3}{\kappa_1} \right) + \kappa_3 I \right] + \frac{\kappa_2}{\kappa_1 - \kappa_2 - \kappa_3} \left[\frac{\kappa_1 - \kappa_3}{\kappa_1} e^{-\kappa_1 I} - \frac{\kappa_1 \kappa_2}{(\kappa_2 + \kappa_3)^2} e^{(\kappa_2 + \kappa_3)I} \right] \quad (4)$$

This kinetic model represents the intensity dependences very accurately, as the successful simultaneous fit of Equation (3) to the triplet data and of Equation (4) to the electron data shows (Figure 1b). The ionization quantum yield ϕ_{ion} of the MLCT triplet species is linearly related to the constant κ_2 divided by the known^[9a] extinction coefficient ϵ_{T} of $^*[\text{Ru}(\text{bpy})_3]^{2+}$.^[6] However, to eliminate inner-filter effects we used the excitation of $[\text{Ru}(\text{bpy})_3]^{2+}$, for which the quantum yield is one,^[8, 9b] as a chemical actinometer, and calculated ϕ_{ion} from the best-fit constants κ_1 and κ_2 , ϵ_{T} , and the ground-state extinction coefficient ϵ_{G} with Equation (5). In this way, we

$$\phi_{\text{ion}} = \frac{\kappa_2 \epsilon_{\text{G}}}{\kappa_1 \epsilon_{\text{T}}} \quad (5)$$

arrived at a value of $0.016 \pm 10\%$ for ϕ_{ion} . Ionization of the MLCT-triplet species $^*[\text{Ru}(\text{bpy})_3]^{2+}$ is thus an order of magnitude more efficient than previously thought.^[5a]

With light of 355 nm wavelength, quite similar results were obtained. Because the absorption properties are more favorable at this wavelength, the turnover was as high as 70%. The quantum yield of ionization was found to be comparable to

that at 308 nm. When 308 and 355 nm irradiation wavelengths are used in conjunction, the electron yield exceeds 100% relative to c_0 . The system does not saturate under these conditions; even above 100%, the electron concentration increases linearly with the laser intensity. Both observations are further evidence of a catalytic cycle.

The photoreaction investigated provides an interesting example of a mechanism in which an electronically excited species, $^*[\text{Ru}(\text{bpy})_3]^{2+}$, acts as a catalyst. As a consequence of the cyclic mechanism, the yield of electrons is not limited by the exhaustion of their precursor $^*[\text{Ru}(\text{bpy})_3]^{2+}$. The reported^[5b-d] increase by a factor of 2–3 in the electron yield, when $[\text{Ru}(\text{bpy})_3]^{2+}$ is photolyzed in a micellar environment, might well be caused by an analogous photoreaction of $[\text{Ru}(\text{bpy})_3]^{3+}$ with a sodium dodecylsulfate molecule instead of a water molecule. Also, the recently reported short-time (<5 ns) anomaly of the luminescence decay of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ at high light intensities, which is characterized by an additional rising component and was attributed to formation of a dd excited state,^[11] would find a natural explanation in the described photoreaction of $[\text{Ru}(\text{bpy})_3]^{3+}$ —the presence of which is unavoidable under these circumstances—to give $^*[\text{Ru}(\text{bpy})_3]^{2+}$.

Experimental Section

Laser flash photolysis was performed with an excimer laser at 308 nm, pulse width 25 ns, and/or an Nd:YAG laser at 355 or 532 nm, pulse width 5 ns. Our setup^[12] allows one- and two-pulse (i.e., two-color) experiments and very high excitation intensities. Aqueous solutions of $[\text{Ru}(\text{bpy})_3]^{2+}$ (typically, $3 \times 10^{-5} \text{ M}$) at neutral pH were degassed and used under argon in a flow cell.

At 532 nm, the only photochemical reaction (even at our highest laser intensity, about 540 mJ cm^{-2}) is formation of $^*[\text{Ru}(\text{bpy})_3]^{2+}$, which reveals its presence by its luminescence (emission range 540–760 nm, maximum at 610 nm) and quantitatively decays to the ground state $[\text{Ru}(\text{bpy})_3]^{2+}$.^[11] At 308 or 355 nm, photolysis of $[\text{Ru}(\text{bpy})_3]^{2+}$ is accompanied by exactly the same luminescence spectrum, so $^*[\text{Ru}(\text{bpy})_3]^{2+}$ is the only emitting species in our system. The absolute concentration of $^*[\text{Ru}(\text{bpy})_3]^{2+}$ was obtained from the measured luminescence intensity at 610 nm by a calibration adapted from the literature.^[9b] Inner-filter effects on the luminescence were not observed.

Absorption measurements gave no evidence for the occurrence of species other than $[\text{Ru}(\text{bpy})_3]^{2+}$, $^*[\text{Ru}(\text{bpy})_3]^{2+}$, the oxidized complex $[\text{Ru}(\text{bpy})_3]^{3+}$, and e_{aq}^- in our reaction. The absolute concentration of e_{aq}^- was measured at 830 nm, where its extinction coefficient is still high, but no $^*[\text{Ru}(\text{bpy})_3]^{2+}$ luminescence interferes. ϵ_{830} was determined relative to the absorption maximum, for which the extinction coefficient was taken from ref. [2]. Difference experiments were necessary because $^*[\text{Ru}(\text{bpy})_3]^{2+}$ also absorbs weakly at 830 nm.^[9b] After recording a series of intensity-dependent measurements, the solution was saturated with nitrous oxide, and the series was then immediately repeated with all other parameters kept constant. The electron absorption is the difference of two corresponding experiments at the same excitation intensity, one with N_2O and the other without. In N_2O saturated solution, the electrons are scavenged within a few nanoseconds, and converted into nonabsorbing species; the reaction is not otherwise affected, as shown by the unchanged luminescence of $^*[\text{Ru}(\text{bpy})_3]^{2+}$.

$[\text{Ru}(\text{bpy})_3]^{3+}$ was prepared and purified according to the literature method.^[3] Alternatively, it was prepared in situ by oxidation of $[\text{Ru}(\text{bpy})_3]^{2+}$ with lead(IV) dioxide or cerium(IV),^[13] with a slight excess of the oxidant. It was used in acidic solution (pH 0), in which it is sufficiently stable for our measurements. Protons rapidly scavenge e_{aq}^- ,^[12] but do not influence our photoreaction in any other way. This was ascertained by control experiments on $[\text{Ru}(\text{bpy})_3]^{2+}$, which gave practically the same intensity dependence of the triplet luminescence, regardless of pH.

The scavenging experiment with benzoic acid had to be carried out in aerated solution, because the reaction stops at a cyclohexadienyl radical in the absence of oxygen. The luminescence was measured with a Perkin-Elmer LS50B spectrometer (excitation wavelength, 300 nm).

Received: October 10, 2001

Revised: February 7, 2002 [Z 18043]

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Characterization and Photochemistry of the Silane–Aluminum Complex $\text{Al} \cdot \text{SiH}_4$ and Its Photoproducts HAlSiH_3 and AlSiH_3 in a Solid Argon Matrix**

Benjamin Gaertner and Hans-Jörg Himmel*

The activation of C–H or Si–H bonds is an area of both fundamental and industrial interest.^[1] The first transition metal complex with an η^2 -bound SiH_4 group, *cis*-[Mo(η^2 - SiH_4)(CO)(R₂PC₂H₄PR₂)₂] (**1**; R = Ph, *i*Bu, Et),^[2] was synthesized in 1995. Remarkably, in solution **1** is in equilibrium with its tautomer [MoH(SiH₃)(CO)(Et₂PC₂H₄PEt₂)₂], which features a seven-coordinate Mo center, as evidenced by the results of variable-temperature ¹H and ³¹P NMR spectroscopy. Since then other systems have been found such as [(PR₃)₂H₂Ru(SiH₄)RuH₂(PR₃)₂] (R = Cy, *i*Pr), in which the

SiH_4 ligand bridges two dihydridobis(phosphane)ruthenium units.^[3]

On the basis of these remarkable experimental results, such silane complexes have also attracted attention from theorists.^[4] It is commonly agreed that the silane–metal bond comprises a dative bond involving the $\sigma(\text{Si–H})$ orbital and a vacant metal orbital of appropriate symmetry and a $d(\text{M}) \rightarrow \sigma^*(\text{Si–H})$ back donation (M = transition metal). However, for main group elements like Al such an interaction is not plausible; here only participation of p orbitals can be considered, and therefore one expects a much weaker bond between the metal atom and ligand. However, preliminary experiments suggested that such a complex might be of sufficient strength to allow its generation and investigation in solid inert gas matrices at temperatures near 10 K.^[5] Here we report on the results leading to the detailed characterization of $\text{Al} \cdot \text{SiH}_4$ (**A**) and its photoproducts, the Al^{II} species HAlSiH_3 (**B**) and the Al^{I} species AlSiH_3 (**C**) in a solid Ar matrix at 12 K.

Al atoms generated in a Knudsen cell at 1100 °C were codeposited with argon gas doped with 0.1–5 % SiH_4 on a polished copper block kept at 12 K. The matrix was subsequently exposed to several photolysis cycles at different wavelengths and IR spectra were recorded before and after each photolysis. Since some of the observed product absorptions lie close to those of SiH_4 , it proved important to run experiments with very low concentrations of SiH_4 in the matrix (0.1 % SiH_4 in Ar, Figure 1) to narrow widths of the SiH_4 bands. As low concentrations, however, lead to weak signals, experiments were also carried out with high (1.5 % SiH_4 in Ar, Figure 2) concentrations of SiH_4 .

In addition to absorptions of SiH_4 ,^[6] the spectrum taken upon deposition displayed bands of a spontaneously formed product **A** of the reaction of Al atoms with SiH_4 (Figure 1). These bands were located at 2181.1, 2174.5, 2131.4, 901.7, and 892.4 cm^{−1} (most intense). Some of these absorption bands are not visible in the original spectra because they are masked by SiH_4 absorptions; however, they are clearly visible in the difference spectra shown in Figure 1b. Photolysis at $\lambda \approx 410$ nm resulted in the rapid disappearance of these bands, and the appearance of several new absorption bands at 2158.4, 2127.6, 2113.3, 1780.9, and 846.2 cm^{−1}, which all belong to a single second reaction product **B**. The strongest absorption at 1780.9 cm^{−1} lies in a region characteristic of $\nu(\text{Al–H})$ stretching modes in Al^{II} species (HAlNH_2 1761.1,^[7] HAlCH_3 1764/1746,^[8] HAlH 1806.3/1769.5,^[9] and HAlPH_2 1768.2 cm^{−1}^[10]). The absorption at 846.2 cm^{−1} lies in the expected region for $\delta(\text{SiH}_3)$ deformation modes (HHgSiH_3 867.8/871.4 cm^{−1}^[11]).^[12]

Photolysis at $\lambda \approx 580$ nm resulted in the disappearance of the absorptions of **B** and the reappearance of those of **A**. Renewed photolysis, at $\lambda \approx 410$ nm, caused the absorptions of **A** to vanish again and those of **B** to regain most of their initial intensity. Thus **A** and **B** can be interconverted almost reversibly.

Photolysis of the matrix with broadband UV/Vis ($\lambda = 200$ –800 nm) resulted in the decay of the absorptions of **B**. An increase in the concentration of **A** was not observed here, instead two new absorptions appeared at 836.2 and 2151.3 cm^{−1} (Figure 2), which can be assigned to the photo-

[*] Dr. Dr. H.-J. Himmel, Dipl.-Chem. B. Gaertner
Institut für Anorganische Chemie
Universität Karlsruhe (TH)
Engesserstrasse, Geb. 30.45, 76128 Karlsruhe (Germany)
Fax: (+49) 721-608-4854
E-mail: himmel@achpc9.chemie.uni-karlsruhe.de

[**] This work was supported by the Deutschen Forschungsgemeinschaft. We thank Prof. H. Burger, Wuppertal, for the donation of a SiH_3D sample.

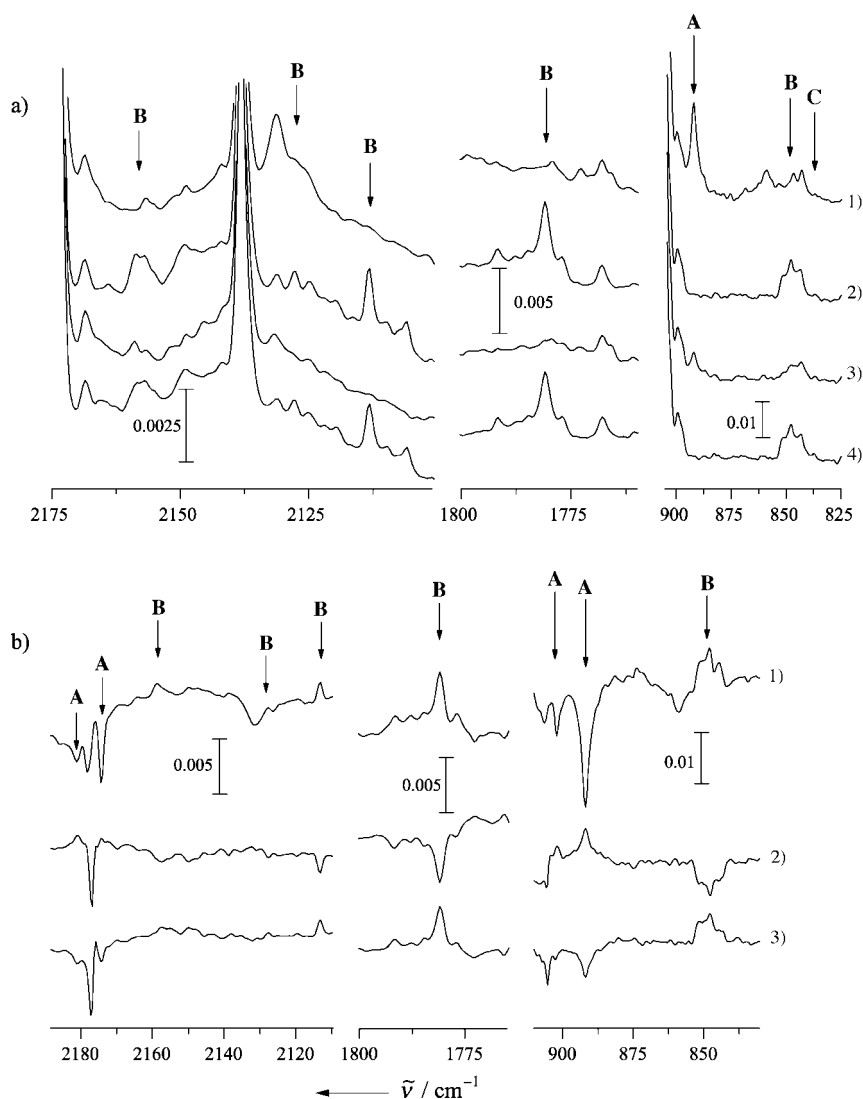


Figure 1. a) IR spectra for the reaction of Al atoms with 0.1 % SiH₄ in an Ar matrix: 1) following deposition; 2) following photolysis at $\lambda \approx 410$ nm; 3) following photolysis at $\lambda \approx 580$ nm, and 4) following renewed photolysis at $\lambda \approx 410$ nm. b) IR difference spectra for the reaction of Al atoms with 0.1 % SiH₄ in an Ar matrix: 1) spectrum following photolysis at $\lambda \approx 410$ nm minus the spectrum following deposition; 2) spectrum following photolysis at $\lambda \approx 580$ nm minus spectrum following photolysis at $\lambda \approx 410$ nm, and 3) spectrum following renewed photolysis at $\lambda \approx 410$ nm minus spectrum following photolysis at $\lambda \approx 580$ nm.

stable product **C**. The more intense of these two absorptions (at 836.2 cm⁻¹) occurs in a region typical for $\delta(\text{SiH}_3)$ deformation modes.

Experiments were performed with SiD₄ or SiD₃H in place of SiH₄, and with different concentrations of SiH₄ and Al in the matrix. The effects of photolysis were similar to those reported for Al/SiH₄, but the IR absorptions of the products were shifted. In the experiments with SiD₄, **A** and **B** absorb at 1580.5, 661.2 (most intense), 639.7, 623.6, and 1543.7, 1297.8, 630.8 cm⁻¹, respectively, in experiments with SiD₃H at 2171.9, 2128.8, 1577.7, 818.1, 813.8, 665.2, 640.8, and 2109.1, 1781.1, 1297.4, 810.4, 631.0 cm⁻¹, respectively.

The experimental results together with the results of detailed quantum-chemical calculations allow us to identify

product **A** as the complex Al·SiH₄ and product **B** as its tautomer HAlSiH₃.^[13] The reaction $\text{A} \rightleftharpoons \text{B}$ is photolytically reversible [Eq. (1)].



Product **C** most likely is the simple Al^I species AlSiH₃. It has been shown in other cases that aluminum hydrides decompose on photolysis with broadband UV/Vis with the loss of H atoms, although this process is endothermic (ca. 220 kJ mol⁻¹ for the decomposition of HAlSiH₃ to AlSiH₃ and H atoms). Thus, for example, AlH₂^[9] and HAlNH₂^[7] decompose photolytically at $\lambda = 200\text{--}800$ nm to give AlH and AlNH₂, respectively.

The experiments also provide evidence for structural details of these species, and these are again consistent with the results of detailed quantum-chemical calculations. The complex Al·SiH₄ has C_{2v} symmetry with the Al atom placed near one of the edges of the slightly distorted SiH₄ tetrahedron resulting in η^2 coordination (Figure 3). In Table 1 the observed wavenumbers are compared with the calculated values. The positions of the $\nu(\text{Si-H})$ stretching fundamentals contain additional, though only qualitative, structural information. Thus two of the $\nu(\text{Si-H})$ modes are red-shifted, and the other two blue-shifted with respect to the asymmetric $\nu(\text{Si-H})$ stretching fundamental in free SiH₄. The obvious inference is that the Si-H bonds directly engaged in the bonding are elongated, while the Si-H

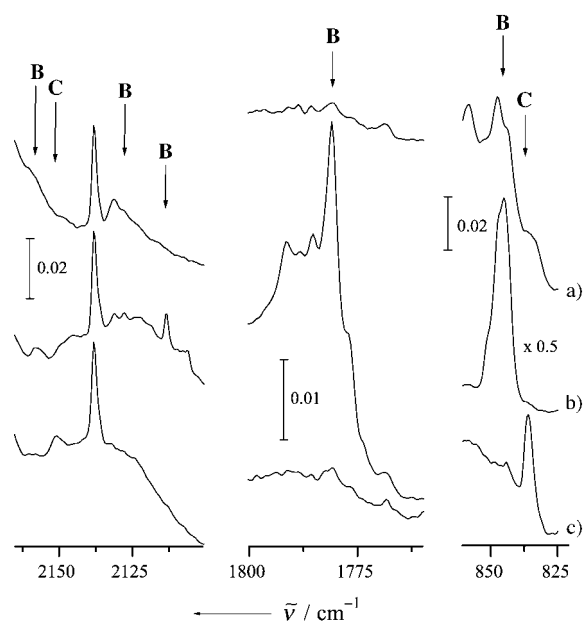


Figure 2. IR spectra for the reaction of Al atoms with 1.5 % SiH₄ in an Ar matrix: a) following deposition; b) following photolysis at $\lambda \approx 410$ nm; c) following photolysis at $\lambda = 200\text{--}800$ nm.

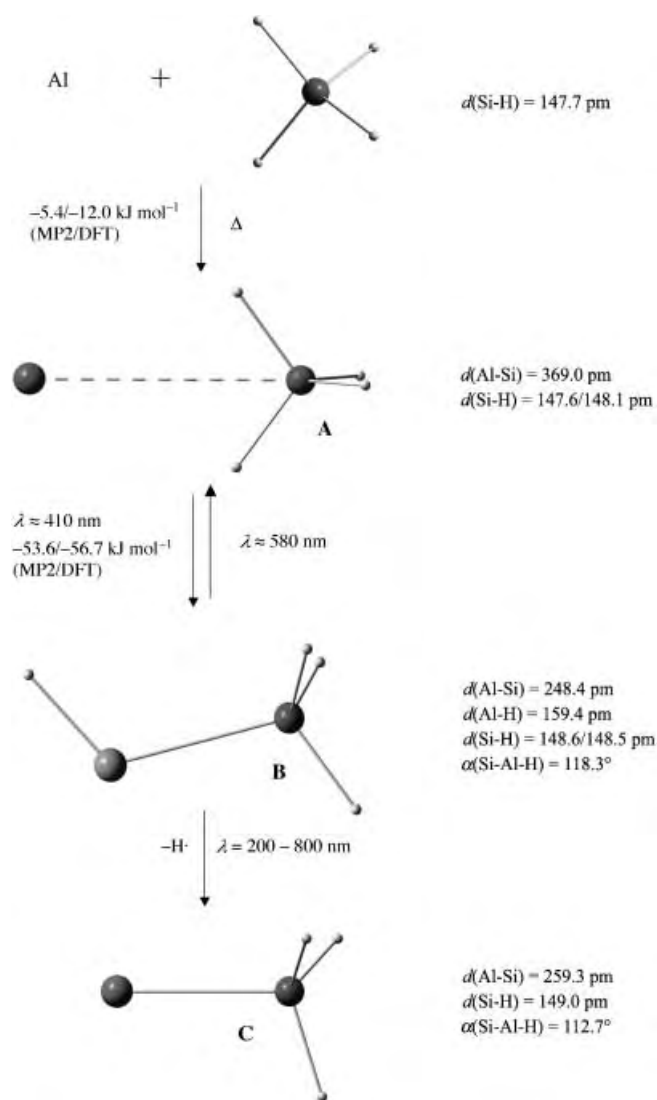


Figure 3. Photolysis of Al atoms with SiH₄ leading to the formation of Al·SiH₄, HAlSiH₃, and AlSiH₃; the calculated structural parameters are given in each case.

bonds pointing away from the aluminum center are shortened because of either a small transfer of charge in the direction SiH₄ → Al or polarization effects. However, this charge trans-

fer, if there is any at all, must be much smaller than in the Al·NH₃ complex, for which it was clearly evidenced by the results of IR^[7] and ESR^[14] studies.^[15]

Our results also show that the insertion product HAlSiH₃ contains no hydrogen bond, as one might expect, but has a structure resembling that of HAlCH₃ with the unpaired electron located near the Al atom (Figure 3). A normal coordinate analysis gave force constants of 182.9 and 107.0 N m⁻¹ for $f(\text{Al-H})$ and $f(\text{Al-Si})$, respectively (cf. 176.3 and 214.4 N m⁻¹ for $f(\text{Al-H})$ and $f(\text{Al-C})$ in HAlCH₃).^[16] The calculated wavenumbers are in excellent agreement with the observed values (Table 1).^[17] AlSiH₃ features only terminal Si-H bonds. A normal coordinate analysis gave a force constant of 120 N m⁻¹ for $f(\text{Al-Si})$ (cf. 175.6 N m⁻¹ for AlCH₃).^[16] According to ab initio MP2 and DFT BP86 methods the photolysis of A to B is exothermic (-53.6 and -56.7 kJ mol⁻¹, respectively; TZVPP basis set). The formation of the Al^I species C as the photostable end product of the reaction is analogous to the previously described reaction of Al with H₂^[9] and of Ga and In with CH₄.^[18]

In summary, cocondensation of Al atoms and SiH₄ in an Ar matrix at 12 K forms spontaneously the complex Al·SiH₄. Our experiments show, in agreement with the results of quantum-chemical calculations, that the silane molecule is η^2 -coordinated to the Al atom. Photolysis at $\lambda \approx 410$ nm causes tautomerization to give the radical HAlSiH₃. However, the complex Al·SiH₄ is reformed by photolysis at $\lambda \approx 580$ nm. With broadband UV/Vis light ($\lambda = 200-800$ nm) HAlSiH₃ decomposes to give the monovalent Al^I species AlSiH₃. All observed reaction products were characterized by IR spectroscopy and quantum-chemical calculations.

Experimental Section

Aluminum (Merck, purity 99.99 %) was evaporated in a boron nitride cell heated resistively to about 1100 °C. The metal vapor was codeposited with an excess of SiH₄-doped argon on a highly polished copper block cooled to 12 K by means of a closed-cycle cryostat (Leybold LB 510). Further details of the relevant matrix assemblies are given in reference [18]. The ratio SiH₄:Ar was typically 0.1:100 and 5:100, while deposition rates were about 2 mmol of matrix gas per hour, continued over a period of 1.5 h. Similar experiments were carried out with SiD₄ and SiD₃H in place of SiH₄. Materials used: SiH₄ (Linde, > 99.99 %), SiD₄ (prepared by reaction of LiAlD₄ with SiCl₄), SiD₃H (prepared by reaction of LiAlD₄ with SiHCl₃).

Table 1. Observed and calculated wavenumbers [cm⁻¹] (IR intensities [km mol⁻¹] in parentheses) for Al·SiH₄, HAlSiH₃, and AlSiH₃.

obsd	Al·SiH ₄ calcd ^[a]	assignment	obsd	HAlSiH ₃ calcd ^[b]	assignment	obsd	AlSiH ₃ calcd ^[c]	assignment
2174.5	2173.7 (254)	$\nu_1(a_1)$	2158.4	2161.9 (79)	$\nu_1(a')$	2151.3	2093.7 (99)	$\nu_1(a_1)$
2131.4	2125.9 (49)	$\nu_2(a_1)$	2113.3	2126.7 (57)	$\nu_2(a')$	836.2	822.4 (211)	$\nu_2(a_1)$
[b]	928.5 (45)	$\nu_3(a_1)$	1780.9	1780.2 (220)	$\nu_3(a')$	[c]	308.2 (52)	$\nu_3(a_1)$
892.4	868.9 (319)	$\nu_4(a_1)$	[b]	904.9 (32)	$\nu_4(a')$	[b]	2106.1 (103)	$\nu_4(e)$
[c]	136.7 (5)	$\nu_5(a_1)$	846.2	836.5 (221)	$\nu_5(a')$	[b]	907.5 (20)	$\nu_5(e)$
[b]	827.0 (0.1)	$\nu_6(a_2)$	[b]	575.5 (48)	$\nu_6(a')$	[c]	302.7 (24)	$\nu_6(e)$
2181.1	2173.1 (71)	$\nu_7(b_1)$	[b]	412.9 (31)	$\nu_7(a')$			
[b]	748.7 (34)	$\nu_8(b_1)$	[c]	345.8 (3)	$\nu_8(a')$			
[c]	282.1 (0.3)	$\nu_9(b_1)$	2127.6	2139.7 (71)	$\nu_9(a'')$			
[c]	2125.8 (19)	$\nu_{10}(b_2)$	[b]	919.1 (28)	$\nu_{10}(a'')$			
901.7	879.3 (58)	$\nu_{11}(b_2)$	[b]	425.1 (16)	$\nu_{11}(a'')$			
[c]	343.8 (2)	$\nu_{12}(b_2)$	[c]	331.4 (9)	$\nu_{12}(a'')$			

[a] DFT calculations: BP86-methods with TZVPP basis set; Al·SiH₄: C_{2v} symmetry, HAlSiH₃: C_s symmetry, C_{3v} symmetry. [b] Intensity too weak to be observed or hidden by SiH₄ absorptions. [c] Outside the range of detection.

and argon (Messer, purity 99.998%). Gas mixtures of argon with the different isotopologues of the silane were prepared by standard manometric methods.

After deposition and IR analysis of the resulting matrix, the sample was exposed to photolysis at different wavelengths and the changes were monitored by IR spectroscopy. A medium-pressure Hg lamp (Philips LP 125) operating at 70 W served as the source of photolyzing radiation. The IR radiation was absorbed by a water filter to minimize any heating effects. IR spectra were recorded in the reflection mode by using a Bruker 113v spectrometer and either a liquid N₂ cooled MCTB or a DTGS detector operating in the range 4000–400 cm⁻¹.

MP2 and DFT calculations using a TZVPP basis set were performed with the aid of the TURBOMOLE^[19] program package.

Received: October 29, 2001

Revised: January 21, 2002 [Z18130]

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- [12] IR absorptions at 2158.4, 2127.6, 2113.3, 1780.9, and 846.2 cm⁻¹ were already observed and assigned to HAlSiH₃ in a previous work (see ref. [5]).
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- [14] P. Kasai, H.-J. Himmel, unpublished results.
- [15] Attempts to study the complex with our UV/Vis spectrometer failed because the light of the spectrometer caused rapid decomposition of the complex as evidenced by IR spectra taken before and after 1 min of exposure to the radiation of the spectrometer. In our setup (spectrometer from Oriel, equipped with a 75 W Xe, HgXe, or Hg arc lamp and a photodiode array detector, Model 77112) the gratings are located between the matrix and the detector and the matrix is exposed to the full radiation of the lamp.
- [16] The normal coordinate analysis were performed by using experimental values for the wavenumbers where available and calculated values for the rest.
- [17] Additional calculations for the deuterated and partially deuterated species were performed. Observed/calculated wavenumbers [cm⁻¹] for the most intense absorptions: Al·SiD₄: 1580.5/1567.7, 639.7/635.3, 661.2/660.6, 623.6/644.6; Al·SiD₃H (both isotopomers): 2171.9/2170.7, 2128.8/2127.7, 1577.7/1569.0, 818.1/818.0, 813.8/811.6, 665.2/659.5, 640.8/636.4; DAlSiD₃: 1543.7/1545.4, 1297.8/1282.2, 630.8/618.1; HAlSiD₃: 1781.1/1780.3, 631.0/618.1; DAlSiD₂H: 2109.1/2134.3–2160.6 (depending on the DAlSiH dihedral angle), 1297.4/1282.2, 810.4/748.7–823.8 (depending on the DAlSiH dihedral angle); AlSiD₃: 618.4/600.3.
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Mesophases of (Bio)Polymer–Silica Particles Inspire a Model for Silica Biomineralization in Diatoms**

Engel G. Vrieling,* Theo P. M. Beelen,
Rutger A. van Santen, and Winfried W. C. Gieskes*

Diatoms, the dominant component of the plant biomass in marine and freshwater environments, are best known for their species-specific cell-wall architecture of amorphous silica.^[1, 2] Synthetic silica-based materials are widely used for industrial purposes, but if nature could be mimicked innovative tailor-made silicas could be produced that approach the architectures of diatom exoskeletons.^[3–5] Silica formation in diatoms seems to be mediated by peptides and polyamines,^[6–8] but how short-term processes control structure-directed silica deposition remains unknown. The size range of the siliceous units and the intracellular location of silica deposition prohibit in situ analysis, while delicate silica intermediates are altered or damaged during isolation and sample preparation prior to structural or biophysical analysis.

Noninvasive X-ray scattering approaches are promising for the study of silica transformation in situ.^[9, 10] To gain insight into silica aggregation and transformation on much larger length scales (up to 6500 nm) in comparison to the well-known silica chemistry on smaller length scales (<10 nm),^[11] we examined X-ray scattering of silica structures at ultrasmall angles (USAXS), which allows reliable statements regarding the geometry and interaction of scattering sources.

Silica formation in diatoms was approximated by synthesizing silica from acidified water glass (tetraethyl orthosilicate is not a natural silica source) in the presence of structure-directing agents; the concentration of dissolved silica and the pH of the solvent were comparable to conditions during silica deposition inside diatoms.^[12] All syntheses were monitored in situ at room temperature and at 90 °C to accelerate the aging

of silica; all end-points were compared with that of a template-free control. In the control (Figure 1a), silica aggregates formed the expected xerogel by reaction-limited cluster–cluster aggregation (RCCA).^[13] The observed slope in the $\lg I - \lg q$ plot of the aged xerogel is -2.58 (Figure 1a), which corresponds to a mass-fractal dimension D_m of 2.58. Surface fractals [D_s , where $D_s = 6 - (-\text{slope})$] are excluded, since they are only physically significant if $2 < D_s < 3$.^[13] The USAXS spectrum of the xerogel revealed no transition points for defining the radius of gyration R_g or primary particle size r_p . Therefore, it can be concluded^[9, 14] that the aggregates were large ($R_g > 6000$ nm with $d = 2\pi q^{-1}$) and composed of primary particles with $r_p \ll 30$ nm.^[9, 10]

Porous silicas can be prepared when polymers are used as structure-directing agents.^[15, 16] In silica directed by poly(ethylene imine) (PEI) distinct straight $\lg I - \lg q$ lines were present (bottom line Figure 1b), with a transition point at $q \approx 0.05$ nm⁻¹. The slope at $q > 0.05$ nm⁻¹ was -2.63 , which almost equals that of the above-mentioned xerogel. However, rather large fractal particles may have formed by interaction of silica with C–C–NH₂ branches of PEI. The size (R_g) of these fractal particles at $q = 0.05$ is approximately 125 nm, roughly that expected with PEI ($M_w = 200\,000$). At $q < 0.05$ nm⁻¹ a less steep slope (-2.03) indicates formation of much larger aggregates ($R_g > 6000$ nm), similar to those in the xerogel. However, when the 125-nm-sized PEI–silica particles are used for the formation of these large aggregates, a strong influence of diffusion limitation results in a much less dense network and a lower D_m (2.03). In silica directed by poly(ethylene glycol) (PEG) a totally different scattering pattern was observed (upper line in Figure 1b), that is, one straight line with slope of -4.0 . This implies the presence of only large ($R_g > 6000$ nm), smooth, nonfractal spherical or vesicle-shaped particles.

Proteinaceous compounds have also been reported to serve as templates.^[17] We used horseradish peroxidase (HRP) and myoglobin (MG) as models, because functional diatomaceous peptides (e.g., silaffins bearing essential polyamine-modified lysine residues^[6–8]) cannot be obtained readily. Because of their size, polyamines and silaffins become completely encapsulated and can no longer direct silica transformations,^[18] although they efficiently induce silica precipitation.^[6, 7] With HRP a straight line covering a wide q range ($0.001 < q < 0.2$ nm⁻¹) was obtained (bottom line in Figure 1c). Similar to the xerogel and PEI-directed silica, this indicates the formation of large fractal aggregates ($R_g > 6000$ nm). However, with HRP the aggregation process resulted in a fractal dimension ($D_m = 2.20$) between the values found for the xerogel and PEI-directed silica, but corresponding to the intermediate size of HRP molecules between those of PEI and primary silica particles. In contrast, the MG-directed silica showed multiple straight-line regions (upper line Figure 1c). At $q > 0.024$ nm⁻¹ the slope of -2.72 corresponds to fractal MG–silica aggregates of about 260 nm in size (R_g at $q = 0.024$). At $q < 0.003$ nm⁻¹ the slope of -2.00 corresponds to much larger diffusion-limited (fractal) aggregates of MG–silica particles ($R_g > 6000$ nm). The short intermediate section ($0.003 < q < 0.024$ nm⁻¹) with a slope of -3.40 represents a transition region.

[*] Dr. E. G. Vrieling,^[+] Dr. W. W. C. Gieskes
Department of Marine Biology
Center for Ecological and Evolutionary Studies
University of Groningen, Biological Center
P.O. Box 14, 9750 AA Haren (The Netherlands)
Fax: (+31)50-363-2261
E-mail: e.g.vrieling@chem.rug.nl
w.w.c.gieskes@biol.rug.nl

Dr. ir. T. P. M. Beelen, Prof. Dr. ir. R. A. van Santen
Laboratory of Inorganic Chemistry and Catalysis
Schuit Institute of Catalysis, Eindhoven University of Technology
P.O. Box 513, 5600 MB, Eindhoven (The Netherlands)
Fax: (+31)40-245-5054

[+] New address:
Groningen Biomolecular Sciences and Biotechnology Institute
University of Groningen, Nijenborgh 4
9747 AG Groningen (The Netherlands)
Fax: (+31)50-363-4165

[**] We thank Dr. T. Narayanan, European Synchrotron Radiation Facility (ESRF, Grenoble, France), and C. Houssin for assistance during measurements. The European Committee granted beamtime (proposal no: SC 595). A. J. van Bennekom of the Netherlands Institute for Sea Research (NIOZ) provided the biogenic silica. E.G.V. was supported by the Netherlands Technology Foundation (STW; grant GFC4983), which is subsidized by the Netherlands Organization for the Advancement of Pure Research (NWO).

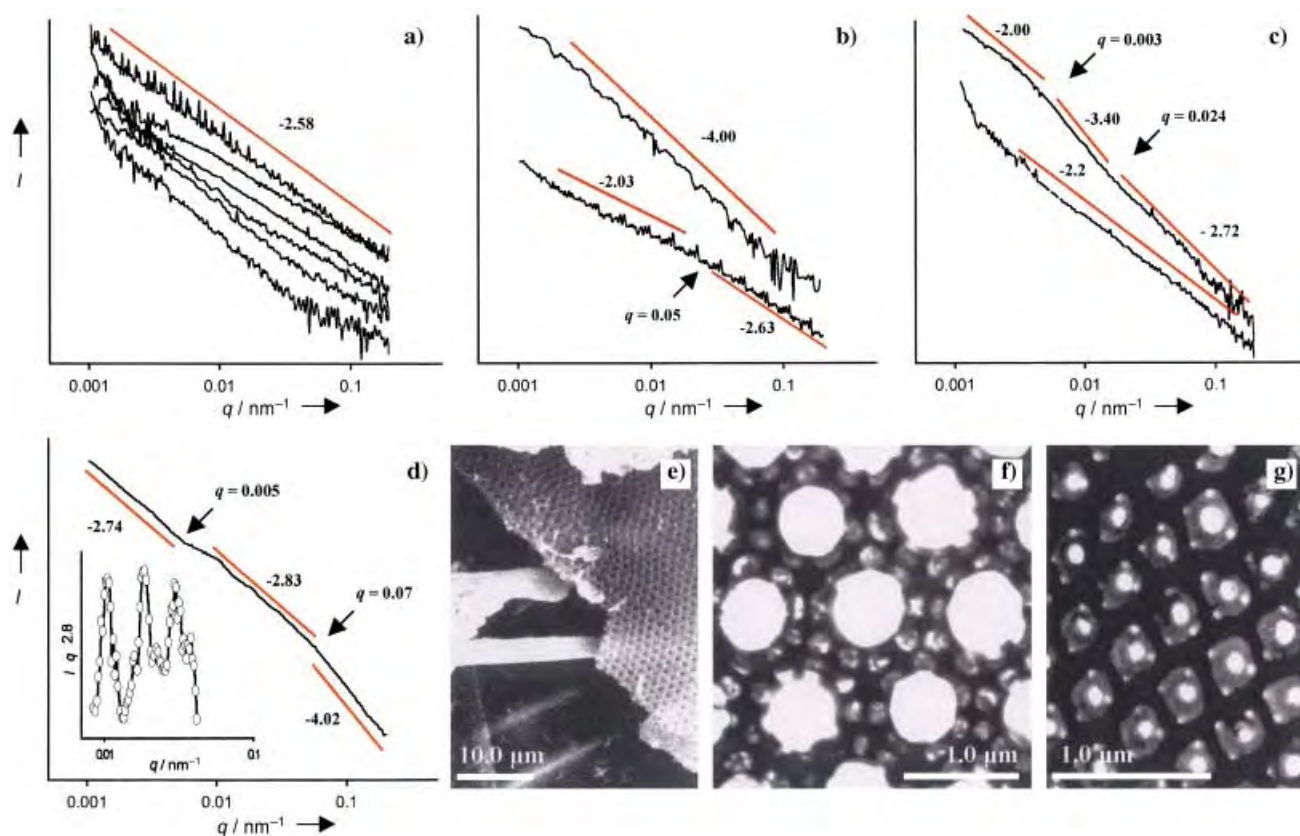


Figure 1. USAXS spectra of time-dependent silica transformations presented as plots of $\lg I$ (scattering intensity) vs $\lg q$ (scattering vector). a) The template-free control experiment resulted in a xerogel; aging at 90 °C (upper 3 lines) followed growth at RT (bottom lines). b, c) Final spectra of template-directed silica syntheses: b) PEI- (bottom line) and PEG-directed silica (upper line), and c) HRP- (bottom line) and MG- directed silica (upper line). d) USAXS spectrum of dried silica from the diatom *Odontella sinensis*, showing distinct regions with slopes of -2.7 , -2.8 , -4.0 . To indicate the position of the small oscillations clearly (inset), the disturbing influence of the slope is cancelled by plotting $Iq^{2.8}$ vs $\lg q$. For clarity, transition points are indicated with arrows, and red lines show the determined slopes. e–g) Electron micrographs at various magnifications of *O. sinensis* silica showing the pore dimensions observed by USAXS in valves (e, f) and girdle bands (g).

The physical principles of USAXS, informative for dimensions and fractal behavior of silica particles in solution, are also applicable to silica powders, where scattering is caused by pores in the solid.^[1, 13] Analysis of silica of the diatom *Odontella sinensis* (Figure 1 d) revealed a pattern as expected for porous diatomaceous silica, which typically has more than one pore dimension and shape.^[1, 2] Electron microscopy (EM) confirmed a distribution of a similar range of pores in the same material (Figure 1 e–g). As expected, the Porod region at $q > 0.08 \text{ nm}^{-1}$ shows a slope of -4.0 in the $\lg I - \lg q$ plot due to scattering of smaller spherical pores. The two other regions in the spectrum, with slopes of -2.8 ($0.01 < q < 0.06 \text{ nm}^{-1}$) and -2.7 ($q < 0.005 \text{ nm}^{-1}$), are here ascribed to combined contributions of several types of pores that are different in size and shape. As observed earlier,^[1] oscillations (inset of Figure 1 d) are also present, although at much larger length scales, between $15 < d < 600 \text{ nm}$ ($0.01 < q < 0.4 \text{ nm}^{-1}$). These oscillations are interpreted as structure factors resulting from well-organized distributions of pores, as could be observed by EM (Figure 1 e–g).

Previous investigations only demonstrated that organic templates build different microporous silicas.^[9, 10, 15–17] Here each polymer or peptide induces formation of distinct silica structures over length scales spanning five decades in size.

This may be the key to an explanation of how diatoms achieve their intricate silica cell-wall architectures, in which the hierarchy of the very different pores of each species covers a similar size range. If diatoms resemble the above-mentioned systems in that they must create silica aggregates whose pores are much larger than a single template molecule, it may be that clustered template molecules come into effect for the larger dimensions, especially since small organic molecules (potentially silaffins, polyamines, and block polypeptides^[6–8, 17]) become completely and irreversibly encapsulated inside silica sol–gels.^[18] In experiments with PEG the formation of silica is influenced by hydrophobic interactions between PEG and the growing silica, which induce transfer of PEG and silicic monomers and oligomers from the solvent into a silica-rich phase, a process called phase separation.^[15] The same was observed during the formation of MCM materials^[16] and can be predicted for polymer–nanoparticle composites.^[19]

In our syntheses, growing silica triggers phase separation by addition of silicic monomers and template molecules to growing silica–template intermediates, while mesophases can direct formation of larger silica structures. This mechanism is the basis of our hypothesis (Figure 2) of how development of the silica architecture proceeds inside the silica-deposition

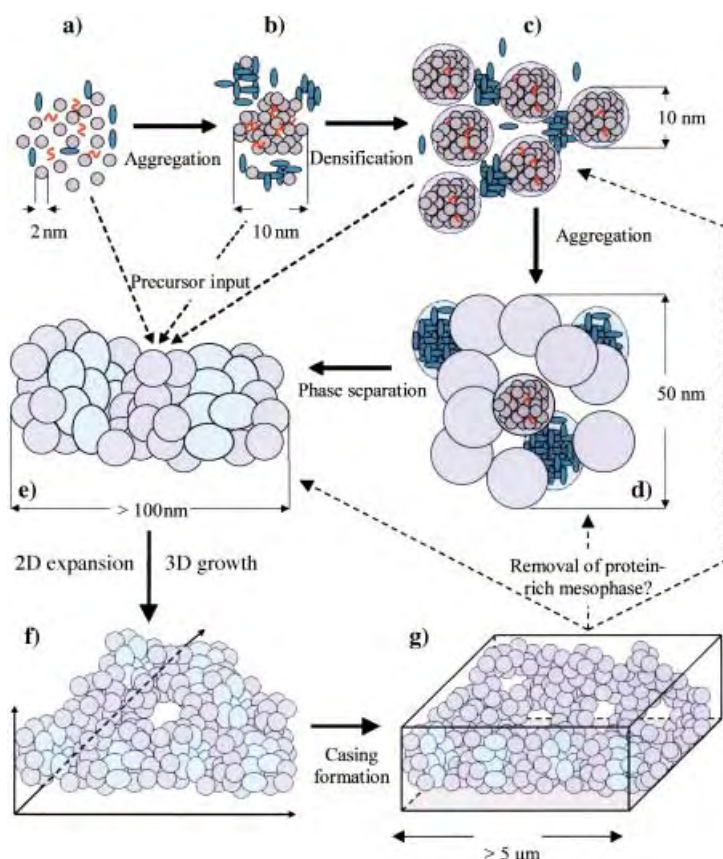


Figure 2. The proposed model of mesophase silica polymerization in diatoms, based on the polymer- and peptide-directed silica syntheses. a) In the immature silica deposition vesicle (SDV) small peptides and/or polyamines (red curved structures), larger organic molecules (green ellipsoids), and silica precursors are present. The latter form small silica sols (gray spheres). b) Silaffins^[6,8] and polyamines^[7] as well as the environmental pH and continuous import of silica precursors in the SDV,^[12] induce fast aggregation of silica. In this process the small organic molecules become completely encapsulated,^[18] while larger peptides interact with the silica and each other. c) Aggregates of silica/silaffins/polyamines densify to larger silica structures (blue circles), which interact with growing aggregates of the larger peptides (the mesophase precursors). d) Continuing aggregation forms larger silica/silica and silica/peptide aggregates (greenish ovals) with structures of about 50 nm in size. e) Densified mesophase particles grow to sizes larger than 100 nm. f) Following continuous input of peptides and silica precursors to the SDV, two-dimensional (2D) expansion and three-dimensional (3D) growth is realized. g) Since large peptides do not remain after the wall has been completed and covered by the casing, we assume that they are somehow removed.

vesicle (SDV) of diatoms. At the onset of valve formation (Figure 2a) silica precursors are transported to the SDV, where the small silaffins and polyamines^[6–8] in an acidic SDV^[12] induce rapid precipitation of silica. Larger peptides interact with the formed silica sols and each other (Figure 2b). Beyond this stage silica densifies, and the larger peptides form large templates as a mesophase (Figure 2c). The larger particles continue to aggregate (Figure 2d) and to densify further (Figure 2e). The dimension of the mesophases depends on the species-specific type or set of peptides that mediate silica polymerization. Continuous delivery of precursors to the SDV allows it to expand two-dimensionally and grow in the third dimension (Figure 2f). When silica parts are completed, we assume that the proteinaceous mesophase somehow is removed in the course of covering the silica with a protective organic casing (Figure 2g). The assumption of

template removal originates from the fact that the few peptides found to be associated with, but not encapsulated in, mature silica cell walls do not play a role in silica polymerization.^[20,21]

Our model suggests that proteinaceous mesophases behave like the wax used in the “cire perdue” (lost wax) method of producing bronze castings. Once silica has been constructed, the proteinaceous phase is removed, leaving a cavity (pore) that is much larger than a single peptide molecule would ever leave. Genetically determined combinations of peptides would generate the differences in pore patterns that are so typically species-specific in diatom cell walls. The next step now is to collect supporting evidence for our hypothesis by following silica syntheses in vitro by using diatomaceous peptides or closely related synthetic compounds.

Experimental Section

Wet silica gels, both with and without templates, were prepared by dropwise addition of 10 mL of water glass solution (6.75% (w/v) SiO₂) to a stirred mixture of HCl (15 mL, 1.0 M), water (10 mL), and template (0.43 g). The templates were poly(ethylene glycol) (PEG; $M_w = 2000$), poly(ethylene imine) (PEI; $M_w = 200000$), myoglobin (MG; $M_w = 17$ kDa), and horseradish peroxidase (HRP; $M_w = 40$ kDa). Immediately after preparation the mixture was transferred to a rotating cell with mica windows ($\varnothing 10$ mm) and a Teflon spacer (thickness 1 mm) for time-resolved USAXS analysis.^[10] After 10–12 h at RT the gels were aged in situ at 90 °C, and again monitored (10–12 h). Silica powder of the diatom *Odontella sinensis* was prepared by low-temperature ashing.^[22] USAXS experiments were performed at the high-brilliance beamline ID02 ($\lambda = 0.099$ nm) at the ESRF (Grenoble, France) by using a Bonse-Hart camera and a configuration with two analyzer crystals to avoid desmearing.^[23] The q range, calibrated with silver behenate, was $0.001 < q < 0.3$ nm⁻¹ ($21 < d < 6280$ nm). Several scans (4–5) over successive 2θ ranges with a sufficient overlap were recorded with different degrees of attenuation of the incident X-ray beam, so that the intensities on the detector were in the linear range. A complete spectrum could be recorded within 15 min. Data sets were corrected for the influence of the rocking curve produced by the setup, background scattering, the small intensity fluctuations of the beam, and the absorption by the reaction mixture. Due to the strong scattering of silica in aggregates and gels, the contribution of water scattering was negligible.^[10] The final scattering intensities were plotted as $\lg I$ vs $\lg q$, with I in arbitrary units and q in nm⁻¹; the latter corresponds to $d = 2\pi/q$ (in nm).

Received: June 13, 2001

Revised: January 9, 2002 [Z17287]

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The Mechanical Properties of Human Angiostatin Can Be Modulated by Means of Its Disulfide Bonds: A Single-Molecule Force-Spectroscopy Study**

Yasser Bustanji and Bruno Samorì*

Human angiostatin 1–5 [Ang(1–5)], a 57 kDa proteolytic fragment of human plasminogen, consists of five compact globular modules called Kringle domains with very similar gross architecture and remarkable sequence homology. They are built around a hydrophobic core and exhibit a triple-loop topology defined by three internal disulfide bonds: cys1–cys80 (1), cys22–cys63 (2), and cys51–cys75 (3) (Figure 1 a).^[1] Here we report on a single-molecule force-spectroscopy study that shows how the redox environment can control the topology and mechanical properties of angiostatin by modifying the extent of pairing of the internal disulfide bonds.

Ang(1–5) molecules were deposited on a polystyrene surface; the tip of a scanning force microscope (SFM) was brought into contact with this surface and retracted after reaching a force of 1 nN. This cycle was repeated many hundreds of times, first under phosphate buffer saline (PBS),

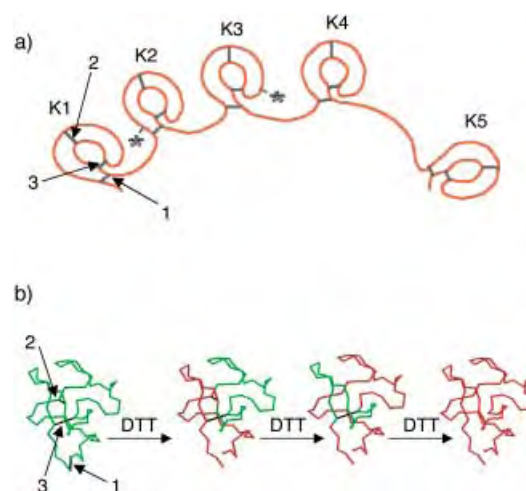


Figure 1. a) Schematic representation of the Ang(1–5) structure with the triple-loop topology of its five Kringle domains (K1–K5), determined in each case by a sequence of three disulfide bonds: cys1–cys80 (1), cys22–cys63 (2), and cys51–cys75 (3). The two asterisks (*) indicate the position of an additional, inter-Kringle disulfide bond. b) Pathway of the sequential reduction of the most exposed (1) and then of the more interior (2) and (3) bonds. This reduction pathway leads to gradually lengthening topological loops (red) that are exposed to the force exerted by the SFM tip at the two ends of the Kringle domain.

and then under different reducing conditions by using dithiothreitol (DTT) in concentrations ranging from 5 to 100 mM. Whenever the tip physically adsorbed and picked up a chain segment of an Ang(1–5) molecule, a molecular bridge was established between the two moving surfaces, and the force acting on this bridge was plotted versus the tip displacement in force curves such as those in Figure 2.

Two representative curves, recorded under PBS buffer prior to any addition of reducing agent, are shown in Figure 2 a. Their profiles are very irregular and typical of deadsorption processes of globular or short inextensible proteins.^[2] These curves do not exhibit the characteristic sawtooth pattern that was previously recognized to be typical of multimodular proteins, and first demonstrated by Gaub and co-workers to result from the sequential stepwise unfolding of their individual domains.^[3] This was due to the fact that Ang(1–5) disulfide bonds acted as mechanical barriers to mechanical unfolding. In fact, being covalent bonds, they can withstand forces up to a few nanonewtons,^[4] that is, much higher than those involved in the experiments reported here, which were in the range of 30–150 pN. Therefore, the mechanical stress exerted on the disulfide bonds, both under nonreducing and reducing conditions (see below), could never succeed in breaking any of them.

The PBS buffer in the fluid cell was then replaced with a 5 mM DTT solution, and force curves were recorded 30 min after DTT injection. This experiment was also performed with 50 and 100 mM DTT, and in the latter case the incubation time was doubled. The force curves recorded under these three sets of reducing conditions exhibited the characteristic sequences of sawtooth peaks (Figure 2 b–d). Each peak resulted from the unfolding of a single module. Each Ang(1–5) module could unfold until an internal unreduced disulfide bond was met along its unfolding pathway. In fact only the disulfide

[*] Prof. B. Samorì, Dr. Y. Bustanji
Dipartimento di Biochimica, Università di Bologna
Via Irnerio 48, 40126 Bologna (Italy)
Fax: (+39)051-2094387
E-mail: samori@alma.unibo.it

[**] This work was supported by Programmi Biotecnologie legge 95/95 (MURST 5%), and MURST PRIN Progetti Biologia Strutturale 1997–1999 and 1999–2001.

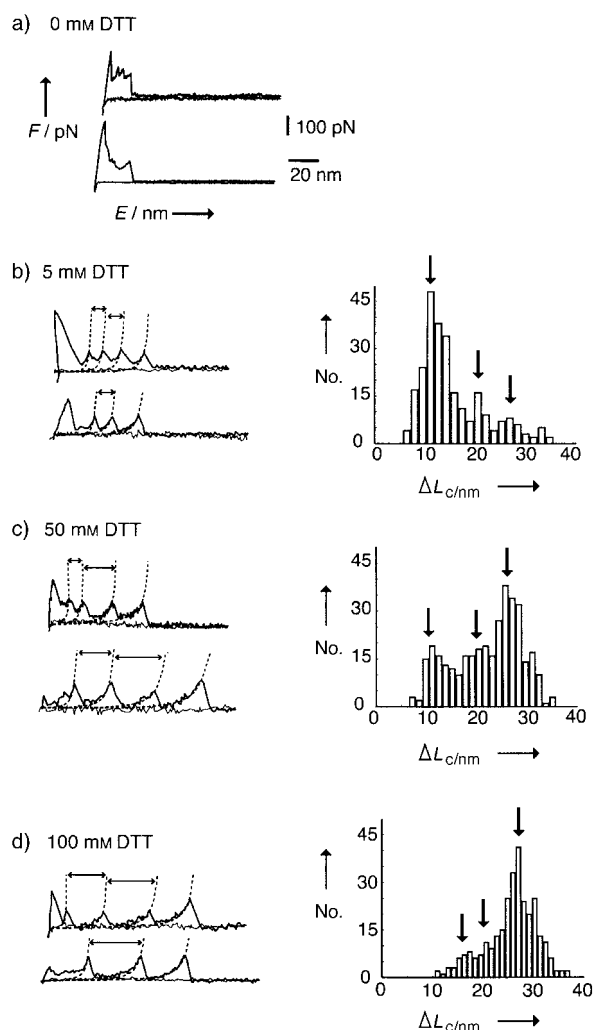


Figure 2. Left: Representative force F vs extension E curves recorded in PBS buffer prior to addition of the reducing agent (DTT) into the fluid cell (a) and in PBS buffer with 5 (b), 50 (c), and 100 mM DTT (d). The length increments of the protein after each unfolding event were estimated by fitting the force curves with the WLC model and assuming a persistence length of 0.36 ± 0.02 nm. This value is in the range of values determined for a modular protein composed of immunoglobulin domains containing an internal disulfide bond.^[5] Right: the relative histograms of the length increments ΔL_c after each unfolding event; they are characterized by three main peaks (↓) that correspond to the different thiol/disulfide intermediates.

bonds that were already chemically opened by DTT no longer acted as points of resistance.^[5] The number of peaks in each force curve ranged from two to four; it was determined by the number of Kringle domains contained in the molecular bridge under tension in each approach–retract cycle, and therefore by the position along the chain at which the protein was picked up by the tip.

As long as the reduction proceeded inside the Kringle domains (Figure 1b), additional topological loops were exposed to the force exerted by the SFM tip, and the length of the resulting unfolded domains increased (Figure 2). The spacing between two subsequent peaks reflects the number of amino acids that each unfolding event added to the total length of the molecular bridge between the tip and the polystyrene substrate.^[6] The behavior of polymers under

stress can be predicted by using the wormlike-chain (WLC) model of entropic polymer elasticity.^[7] This model made it possible to estimate the length increase after each unfolding event, as shown in Figure 2b–d.

The distributions of these length increments (Figure 2, right) were characterized by three peaks centered at about 12, 20, and 27 nm. The heights of these peaks depended on the reducing conditions: after reduction with 5 mM DTT the highest peak was that at about 12 nm, and the other two were much smaller; after reduction with 100 mM DTT the highest was that at 28 nm. The heights of the three peaks were on the same order of magnitude after reduction with 50 mM DTT.

On the basis of the Kringle domain structure (Figure 1b) we could assign these peaks to different thiol/disulfide intermediates. The reduction of the most exposed cys1–cys80 (first) disulfide bond of each Kringle domain opens a topological loop of 40 amino acids that corresponds to an increase in length of 14 nm (Figure 2b). On increasing the concentration of the DTT, reduction can proceed further to include the second and third bonds, and longer sections of the domain can unfold, with length increments of 21 and 29 nm, respectively (Figure 2c,d).

Note that uncertainty still remains in these assignments. Since the unfolding of each domain is blocked by the first unreduced disulfide bond, the peak at about 12 nm could also correspond to domains in which the first and third disulfide bonds, but not the second, were reduced. The disulfide bond between Kringle domains 2 and 3 (Figure 1a) was found to play no role in this dependence of domain topology on the reducing conditions. As an interchain bridge, it is very likely that it was already completely reduced with 5 mM DTT.^[8]

The distributions of intermediates obtained under the different reducing conditions could be estimated from the heights of the three main peaks (see arrows) in the length-increment histograms of Figure 2 only after we had ruled out a potential artifact. These distributions could have been modified during the mechanical unfolding and refolding cycles because of possible thiol/disulfide interchange reactions and/or because of increased accessibility conferred on interior disulfide bonds. We could rule out major contributions from these two possible side reactions because the histograms in Figure 2 did not change significantly after we had chemically trapped the free thiol groups with iodoacetamide. Treatment with this alkylating agent was carried out after reduction with DTT and before recording the force curves in PBS buffer, in this case in the absence of any reducing agent. The length increment distributions of the histograms in Figure 2 can thus be considered to reflect those of intermediates obtained under the different reducing conditions.

The presence of partially reduced intermediates in large amounts after reduction with 50 mM DTT, and still in significant quantities after treatment with 100 mM DTT, demonstrates that the Kringle domain disulfide bonds are not reduced by DTT with an “all-or-none” mechanism, as in other proteins,^[9] but in a sequential manner starting from the most exposed bond (cys1–cys80). This result is in perfect accord with gel-filtration studies on reductive cleavage and denaturation of Kringle domains.^[10]

To our knowledge this is the first report on the use of single-molecule atomic-force spectroscopy to study the reduction pathway of multiple disulfide bonds in proteins and to evaluate the distributions of intermediates obtained under different reducing conditions without separating them and without any blocking and fractionation steps. The characterization of these intermediates has so far been accomplished by first blocking them with reagents such as alkylalkanethiosulfonates and then by fractionation by ion-exchange chromatography, 2D or capillary gel electrophoresis, or gel filtration.^[11] The determination of thiol groups and disulfide bonds in a polythiol systems has always been a very challenging problem.^[12]

The single-molecule force-spectroscopy data presented here show: 1) how a redox environment can modulate the mechanical properties of angiotensin; 2) how this modulation relies, at the single-molecule level, on the extent of reduction of the disulfide bonds; and 3) how, at the level of a large sample of molecules, the distribution of the different thiol/disulfide intermediates after reduction can be estimated by statistical analysis of the force curves.

Experimental Section

Ang(1–5), purchased from Calbiochem with purity greater than 95 %, was adsorbed onto a Petri dish from a 20–100 µg/mL PBS (pH 7.4) buffer solution for 3–5 min and then rinsed with the same buffer. The Petri dish was previously cleaned and exposed to high-energy nitrogen plasma for 15 min. The force-spectroscopy experiments were performed with a Nanoscope IIIa, Digital Instrument, Santa Barbara, CA, with silicon nitride (Si₃N₄) probes (Microlevers, Thermomicroscopes) with a spring constant of 40–55 pN nm⁻¹, determined by a thermal oscillation method.^[13] A velocity of 1 µm s⁻¹ during tip approach and retraction, a loading force of about 1 nN, and a contact time between the tip and the surface of 200 ms were used. We started recording the force curves 30 min after injection of 5 or 50 mM DTT (Aldrich), and 60 min after injection of 100 mM DTT into the fluid cell.

The same experiment was repeated with the following two modifications: First, after reduction with 5, 50, or 100 mM DTT, we injected a 100 mM solution of iodoacetamide (Fluka) into the fluid cell, and allowed it to stand for 20 min. Second, the iodoacetamide solution was subsequently replaced with PBS, under which the force-spectroscopy measurements were then carried out.

Received: July 24, 2001

Revised: January 21, 2002 [Z17590]

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Colorimetric and Fluorometric Detection of Nucleic Acids Using Cationic Polythiophene Derivatives**

Hoang-Anh Ho, Maurice Boissinot, Michel G. Bergeron, Geneviève Corbeil, Kim Doré, Denis Boudreau, and Mario Leclerc*

Simple and reliable sequence-specific methods are needed for the rapid detection of oligonucleotides, to diagnose infections and various genetic diseases. In this regard, interesting optical and electrochemical DNA-hybridization sensors have been proposed.^[1–5] The recognition capabilities of DNA are well established but, to transduce the recognition event into a physically measurable value, a fluorescent or electroactive tag is often bound to the analyte. Electrochemical and optical sensors based on conjugated polymers have also been reported^[6–9] and some oligonucleotide-functionalized conjugated polymers can also transduce hybridization events into an electrical signal without labeling of the oligonucleotide target.^[10–12] The detection relies on a mod-

[*] Prof. Dr. M. Leclerc

Canada Research Chair in Polymer Chemistry
CERSIM, Département de Chimie, Université Laval
Quebec City, Qc, G1 K 7P4 (Canada)
Fax: (+1) 418-656-7916
E-mail: mario.leclerc@chm.ulaval.ca

Prof. Dr. M. Leclerc, Dr. H.-A. Ho, G. Corbeil, K. Doré
Canada Research Chair in Polymer Chemistry
Centre de recherche en sciences et ingénierie des macromolécules
Département de chimie, Université Laval
Quebec City, Qc, G1 K 7P4 (Canada)

Dr. M. Boissinot, Prof. Dr. M. G. Bergeron
Centre de recherche en infectiologie
Centre hospitalier universitaire de Québec
Pavillon CHUL, Université Laval
Quebec City, Qc, G1V 4G2 (Canada)

K. Doré, Prof. Dr. D. Boudreau
Centre de recherche en optique, photonique et laser
Département de chimie, Université Laval
Quebec City, Qc, G1 K 7P4 (Canada)

[**] This work was supported by the Natural Sciences and Engineering Research Council of Canada (D.B. and M.L.), the Canada Research Chair Program (M.L.), the Canadian Institutes of Health Research (M.G.B.) and Infectio Diagnostic (IDI) Inc.

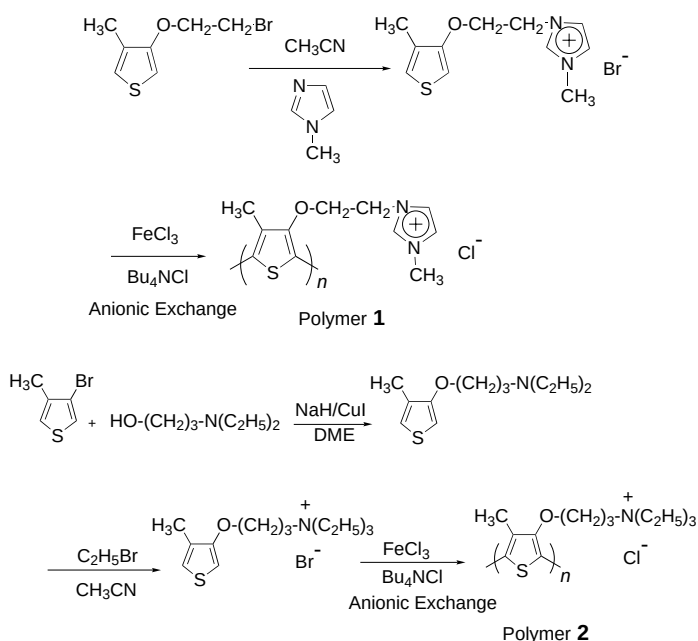


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ification of the electrical properties of the conjugated polymers, through the capture of the complementary oligonucleotides. An assay that does not require any chemical manipulation of nucleic acids or complex reaction mixtures would be greatly advantageous.

We report here new water-soluble cationic polythiophene derivatives, which can easily transduce oligonucleotide hybridization with a specific 20-mer capture probe into a clear optical (colorimetric or fluorometric) output. This simple, rapid, and versatile methodology does not require any chemical reaction of the probes or the analytes; it is based on different electrostatic interactions and conformational structures between electroactive and photoactive cationic poly(3-alkoxy-4-methylthiophene)s, and single-stranded oligonucleotides or double-stranded (hybridized) nucleic acids.

We prepared the cationic, water-soluble, electroactive, and photoactive polymers **1** and **2** (Scheme 1). The new monomers were obtained using straightforward reactions^[13–16] and



Scheme 1. Synthesis of polymers **1** and **2**. Experimental procedures and characterization data are in the Supporting Information.

the related polymers were prepared from an oxidative polymerization in chloroform, by using FeCl_3 as the oxidizing agent.^[17] As reported for anionic poly(3-alkoxy-4-methylthiophene)s,^[17, 18] this method of polymerization usually yields well-defined polymers with a number-average molecular weight of about 6–10 kDa and a polydispersity index of about 1.2–2.9. However, as recently reported by Lukkari et al.^[18] for similar cationic polythiophenes, attempts to determine the molecular weight of the present polythiophenes by size-exclusion chromatography (SEC) experiments were not successful, presumably because SEC columns contain some anionic

groups, which lead to a strong adsorption of these cationic polymers. Matrix-assisted laser-desorption/ionization time-of-flight (MALDI-TOF) spectroscopic measurements were also unsuccessful.

As expected, the resulting polymers **1** and **2** are soluble in aqueous solutions. For instance, at 55 °C, aqueous solutions (0.1 M NaCl or 10 mM tris(hydroxymethyl)aminomethane (Tris) buffer/0.1 M NaCl) of the cationic polymer **1** are yellow ($\lambda_{\text{max}} = 397 \text{ nm}$; Figure 1 A,a and B,a). This absorption maxi-

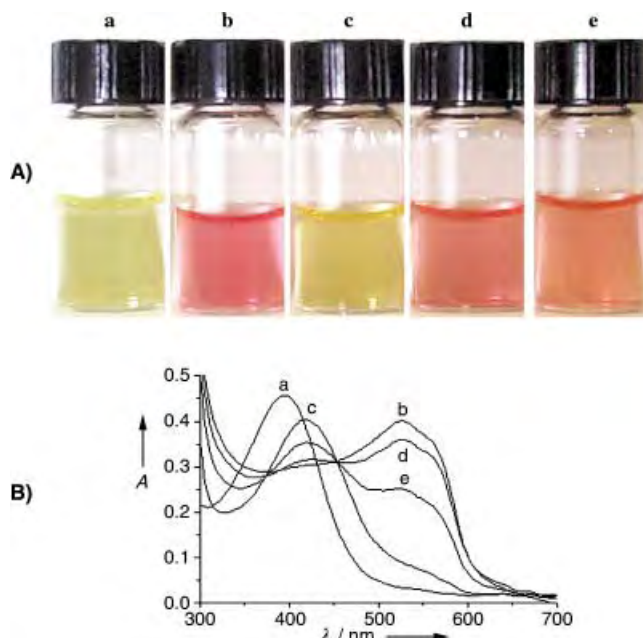


Figure 1. A) Photographs of solutions ($7.9 \times 10^{-5} \text{ M}$, on a monomeric unit basis) of a) polymer **1**, b) polymer **1/X1** duplex, c) polymer **1/X1/Y1** triplex, d) polymer **1/X1/Y2** mixture, and e) polymer **1/X1/Y3** mixture after 5 min of mixing at 55 °C in 0.1 M NaCl/ H_2O . B) UV/Vis absorption spectra corresponding to the different assays in photograph A.

mum at a short wavelength is related to a random-coil conformation of the polythiophene derivative, as any twisting of the conjugated backbone leads to a decrease in the effective conjugation length^[6] (Figure 2). As with any water-soluble cationic polyelectrolytes, these polythiophene deriv-

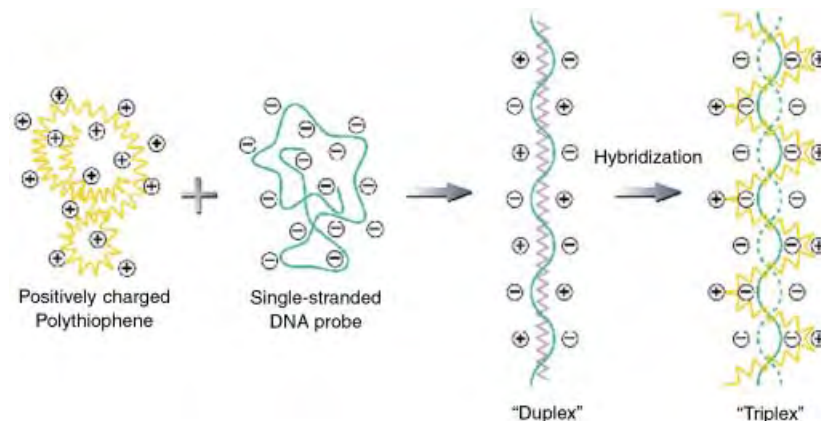


Figure 2. Schematic description of the formation of polythiophene/single-stranded nucleic acid duplex and polythiophene/hybridized nucleic acid triplex forms.

atives can form strong complexes with negatively charged oligomers and polymers.^[19] We report here the use of three types of negatively charged oligonucleotides: a capture-probe sequence (**X1**: 5'-CATGATTGAACCATCCACCA-3'), a perfect complementary target (**Y1**: 3'-GTACTAACTTGGTAGGTGGT-5'), a two-mismatch complementary target (**Y2**: 3'-GTACTAACTTCGAAGGTGGT-5'), and a one-mismatch complementary target (**Y3**: 3'-GTACTAACTTCGTAGGTGGT-5'). The oligonucleotides **X1** and **Y1** are a specific oligonucleotide pair for *Candida albicans*, **Y2** is a specific oligonucleotide for *Candida dubliniensis*, and **Y3** is a variant designed to have single mismatches with either *C. albicans* or *C. dubliniensis* sequences. Upon addition of 1.0 equivalent, on a monomer unit basis (the concentrations of the 20-mer oligonucleotides are therefore a twentieth of those reported for the synthetic polydisperse polythiophene, which are given per repeat unit), of capture oligonucleotide **X1**, the mixture becomes red ($\lambda_{\text{max}} = 527 \text{ nm}$) within 5 min (Figure 1A,b and B,b), because of the formation of a so-called duplex between the polythiophene and the oligonucleotide probe (see Figure 2). However, it is difficult to determine whether these duplexes are isolated species or form aggregates. Precipitation occurs after several hours. After 5 min of mixing in the presence of 1.0 equivalent of the complementary oligonucleotide **Y1**, the solution becomes yellow ($\lambda_{\text{max}} = 421 \text{ nm}$) (Figure 1A,c and B,c); presumably caused by the formation of a new complex termed a triplex (Figure 2), formed by complexation of the polymer with the hybridized nucleic acids. No precipitation was observed, even after several hours. Further addition of 1.0 equivalent of the probe oligonucleotide **X1** does not induce any color change, either in the duplex or in the triplex. The same is true for the addition of another 1.0 equivalent of the target oligonucleotide **Y1** to the triplex. These results highlight the stronger affinity of the cationic polymer towards double-stranded oligonucleotides. It is also important to note that duplexes are unstable at temperatures higher than 65 °C, whereas triplexes do not form at temperatures lower than 45 °C. Very similar results have been obtained with different probe and target oligonucleotides and with polymer **2**.

On the basis of previous studies performed on thermo-chromic, solvatochromic, and affinitychromic (changing color upon binding) regioregular poly(3-alkoxy-4-methylthiophene)s,^[6] it is believed that these colorimetric effects are made possible because of a different conformational structure of the conjugated polymer in the duplex form (highly conjugated, planar conformation) compared to that observed in the triplex form (less conjugated, nonplanar conformation; Figure 2). In addition, as shown in Figure 3, circular-dichroism (CD) measurements did not reveal any optical activity for polymer **1** in its random coil and duplex forms, but showed a bisignate CD spectrum centered at 420 nm in the triplex form, characteristic of a right-handed helical orientation of the polythiophene backbone.^[9] Such a right-handed helical structure is compatible with the binding of the polymer to the negatively charged phosphate backbone of DNA. The presence of a CD signal only in the spectrum of the triplex form, combined with the presence of a clear isosbestic point as a function of the amount of the complementary strand (not

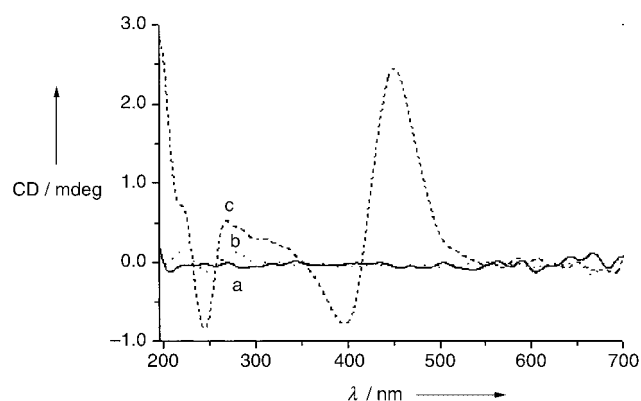


Figure 3. Circular dichroism spectrum of a solution ($1.2 \times 10^{-4} \text{ M}$, on a monomer unit basis) of a) polymer **1**, of b) polymer **1/X1** duplex, and c) polymer **1/X1/Y1** triplex, at 55 °C, in 10 mM Tris-buffered aqueous solution containing 0.1 M NaCl (pH 8).

shown here), indicates the coexistence of only two distinct conformational structures (triplex and duplex) for the polythiophene. In addition, these measurements indicate that triplexes are stable up to 80 °C. This difference in thermal stability between duplexes and triplexes could be extremely useful for the future design of solid-state sensors where the probes could be covalently attached to different substrates.

To verify the specificity of this polymeric optical transducer in the presence of imperfect or incomplete hybridizations, different oligonucleotides (20-mers differing by only 1 or 2 nucleotides) were investigated. A very distinct, stable (up to several hours), and reproducible UV/Vis absorption spectrum is observed in the case of oligonucleotide targets with two mismatches (**Y2**; Figure 1B,d) when compared to perfect hybridization (Figure 1B,c). It is also possible to distinguish only one mismatch (Figure 1A,e and B,e). In the case of one mismatch, the complexation kinetics were monitored; after 30–60 min at 55 °C, the color changed back to yellow. However, it is possible to stop the color change after 5 min by cooling the solution to room temperature. Therefore, it is easy to distinguish one or two mismatches from no mismatch in 5 min. Once again, it is interesting to note that the spectra of duplex and triplex forms show an isosbestic point, which indicates the presence of only two distinct conformational structures for the polymeric transducer. The detection limit of this colorimetric method is about 1×10^{13} molecules of oligonucleotide (20-mers), in a total volume of 100 μL (which is a concentration of $2 \times 10^{-7} \text{ M}$).

A fluorometric detection of oligonucleotide hybridization is also possible since the fluorescence of poly(3-alkoxy-4-methylthiophene)s is quenched in the planar, aggregated form.^[6] At 55 °C, the yellow form of polymer **1** is fluorescent (quantum yield of 0.03, measured against polythiophene standards,^[6] with a maximum of emission at 530 nm, Figure 4,a) but upon addition of 1.0 equivalent of a negatively charged capture oligonucleotide probe **X1**, the fluorescence intensity decreases and the maximum of emission is slightly red-shifted (Figure 4,b). When hybridization with the complementary strand **Y1** takes place, the formation of a polymeric triplex leads to a fivefold rise in fluorescence intensity (Figure 4,c). Interestingly, upon addition of one (Figure 4,d)

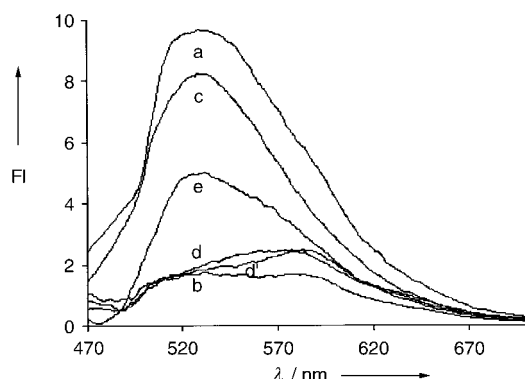


Figure 4. Fluorescence spectrum (FI = fluorescence intensity) of a solution (2.0×10^{-7} M, on a monomer unit basis) of a) polymer **1**, b) polymer **1/X1** duplex, c) polymer **1/X1/Y1** triplex, d) polymer **1/X1/Y2** mixture, d') polymer **1/X1/Y2** (100 equivalents) mixture and e) polymer **1/X1/Y3** mixture at 55°C , in 10 mM Tris buffer containing 0.1 M NaCl (pH 8).

or even 100 equivalents (Figure 4,d') of the target oligonucleotide with two mismatches (**Y2**), the fluorescence intensity is not significantly modified. It is even possible to distinguish oligonucleotides with one mismatch (Figure 4,e). By measuring the fluorescence intensity at 530 nm (without recording the entire emission spectrum), it is possible to detect the presence of as few as 3×10^6 molecules of the perfect complementary oligonucleotide (20-mers) in a volume of 200 μL (this is a concentration of 2×10^{-14} M). Moreover, covalent attachment of the oligonucleotide to the fluorescent conjugated polymer, or use of an optimized fluorescence detection procedure based on a high-intensity blue diode (as the excitation source) and a nondispersive, interference filter-based system should yield even more sensitive and more specific detection capability. The electroactivity of these cationic polythiophene derivatives in aqueous solutions could also be exploited for the detection of DNA-hybridization events.

In conclusion, a novel methodology that allows simple optical (colorimetric or fluorometric) detection of nucleic acids has been developed. This rapid, selective, sensitive (as few as 3×10^6 molecules of oligonucleotide in 200 μL can be detected), and versatile method does not require any chemical reaction of the probes or the analytes and is based on conformational modifications of the conjugated backbone of cationic poly(3-alkoxy-4-methylthiophene)s, when mixed with single-stranded or double-stranded (hybridized) oligonucleotides. This procedure could provide inexpensive methodologies for the rapid detection and identification of nucleic acids.

Received: November 9, 2001
Revised: February 18, 2002 [Z18191]

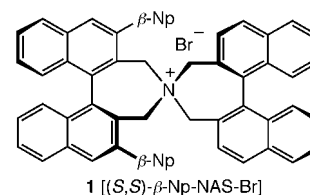
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Conformationally Flexible, Chiral Quaternary Ammonium Bromides for Asymmetric Phase-Transfer Catalysis**

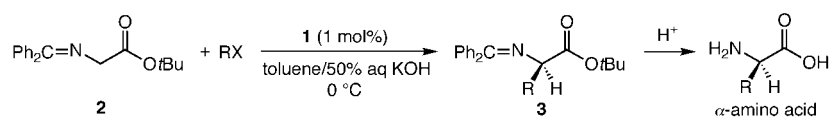
Takashi Ooi, Yukitaka Uematsu, Minoru Kameda, and Keiji Maruoka*

As clearly demonstrated by a number of notable recent successes, the use of phase-transfer catalysis for the preparation of chiral, nonracemic organic compounds from prochiral substrates using chiral catalysts such as optically pure quaternary ammonium salts has become a field of growing importance.^[1,2] We recently contributed to this area by introducing chiral C_2 -symmetric quaternary ammonium bromides of type **1** which efficiently catalyze the phase-transfer



[*] Prof. K. Maruoka, Dr. T. Ooi, Y. Uematsu, M. Kameda
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto, 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[**] This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. M.K. is grateful to the Japan Society for the Promotion of Science for Young Scientists for a Research Fellowship.



Scheme 1. Practical asymmetric synthesis of α -amino acids by the phase-transfer alkylation of the glycine Schiff base **2** catalyzed by the chiral C_2 -symmetric quaternary ammonium bromide **1**.

alkylation of protected glycine derivative **2** with excellent enantioselectivities, providing a practical method for the asymmetric synthesis of both natural and unnatural α -amino acids (Scheme 1).^[3, 4] Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of our catalysts and seems essential for attaining sufficient reactivity and enantioselectivity, it also imposes obvious limitations on the catalyst design due to the imperative use of the two chiral binaphthyl moieties and the difficulty of their fruitful modifications. Accordingly, a more simple yet flexible strategy for the molecular design of chiral catalysts is required to solve this intrinsic dilemma. Herein we disclose a new C_2 -symmetric chiral quaternary ammonium bromide **4** that possesses an achiral, conformationally flexible biphenyl subunit, which exhibits high chiral efficiency by taking advantage of the considerable difference of activity between the diastereomeric homo- and heterochiral isomers through rapid conformational interconversion.

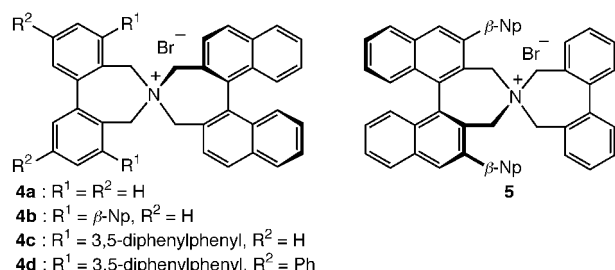
First, we assembled the quaternary ammonium bromide **4a** and evaluated its reactivity and selectivity using the phase-transfer catalytic benzylation of **2** as a benchmark reaction. Treatment of **2** with benzyl bromide (1.2 equiv) in 50% aqueous KOH/toluene (v/v 1:3) in the presence of 1 mol % of

ascribable to the considerable difference of catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral-**4** or -**5** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce **3** ($R = \text{CH}_2\text{Ph}$) with high enantiomeric excess, whereas heterochiral-**4** or -**5** displays low reactivity and stereoselectivity (Scheme 2).^[6, 7] To gain supportive evidence of this, we prepared the heterochiral quaternary ammonium

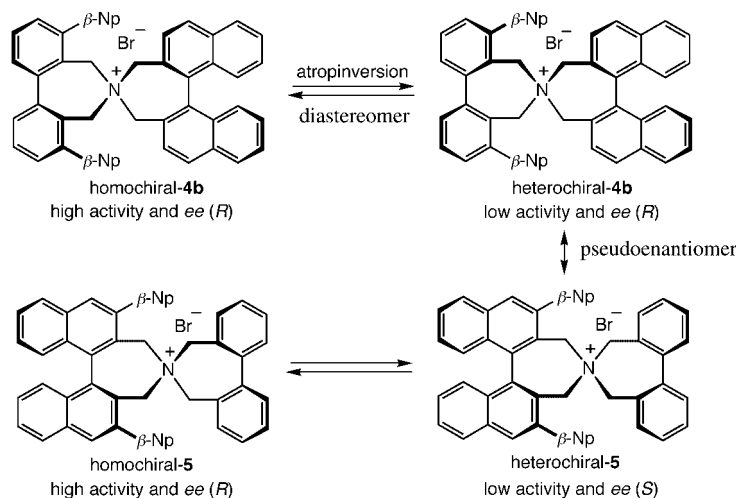
Table 1. Catalytic enantioselective phase-transfer alkylation with conformationally interconvertible catalyst.^[a]

Entry	RX	Catalyst	Reaction time [h]	Yield ^[b] [%]	ee ^[c] [%]	Config. ^[d]
1	PhCH ₂ Br	4a	36	62	64	<i>R</i>
2	PhCH ₂ Br	4b	18	85	87	<i>R</i>
3	PhCH ₂ Br	5	8.5	87	83	<i>R</i>
4	PhCH ₂ Br	4c	27	95	92	<i>R</i>
5	PhCH ₂ Br	4d	48	81	95	<i>R</i>
6	PhCH ₂ Br	4d	16	87	94	<i>R</i> ^[e]
7	CH ₂ =CHCH ₂ Br	4d	16	85	93	<i>R</i> ^[e]
8	EtI	4d	15	61	93	<i>R</i> ^[e,f]
9		4d	19	91	93	<i>R</i> ^[e]

[a] Unless otherwise specified, the reaction was carried out with **2** (0.5 mmol) and 1.2 equiv of RX in the presence of 1 mol % of **4** or **5** in 50% aqueous KOH/toluene (v/v 1:3) under the given reaction conditions under argon atmosphere. [b] Yield of isolated product. [c] Enantiopurity of **3** was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD for entries 1–8 and Chiralpak AD for entry 9) with hexane/2-propanol as solvent. [d] Absolute configuration of **3** was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.^[1b] [e] Three equivalents of CsOH·H₂O in water (29.2 μL) were used as a base and the reaction was performed at -15°C . [f] Five equivalents of alkyl halide were used.

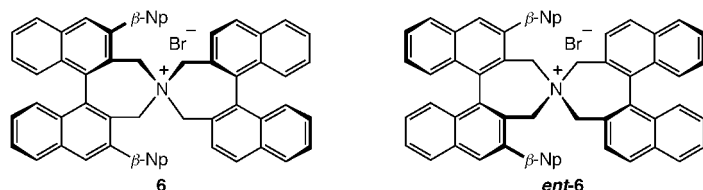


4a at 0°C for 36 h under an argon atmosphere resulted in formation of **3** ($R = \text{CH}_2\text{Ph}$) in 62% yield.^[5] Fortunately, appreciable enantioselectivity (64% *ee*) was attained and the absolute configuration was assigned to be *R* as shown in Table 1 (entry 1). Based on this result, we next examined the catalyst **4b**, which has a β -naphthyl group at the 3,3'-position of the flexible biphenyl moiety, and found, as hoped, that both chemical yield and the enantioselectivity were improved to 85%, 87% *ee* (*R*) (Table 1, entry 2). The reaction was also smoothly catalyzed by the chiral ammonium bromide **5**, which has β -naphthyl ($\beta\text{-Np}$) substituents on the chiral binaphthyl framework, giving **3** ($R = \text{CH}_2\text{Ph}$) in 87%, 83% *ee* with the same *R* configuration (Table 1, entry 3). Here, we assumed that the origin of the observed chiral efficiency could be



Scheme 2. Expected conformational interconversion of **4b** and **5**.

bromide **6** and found that the alkylation of **2** with benzyl bromide (1.2 equiv) and 1 mol % of **6** under similar conditions proceeded slowly, and, after 60 h, gave rise to the corresponding benzylation product **3** ($R = \text{CH}_2\text{Ph}$) in 47 % yield with low enantiomeric excess (11 % *ee*, *R*).^[3a] We also confirmed that



ent-**6** exerted comparable catalytic activity as **6** in the phase-transfer benzylation of **2** with the opposite sense of asymmetric induction (51 %, 11 % *ee*, *S*). Furthermore, the benzylation of **2** with 0.5 mol % each of **1** and **6** under otherwise similar phase-transfer conditions at 0 °C for 13 h afforded **3** ($R = \text{CH}_2\text{Ph}$) in 88 % yield with 94 % *ee* (*R*), and the use of 0.5 mol % each of **1** and *ent*-**6** as catalyst, though a mismatched combination in terms of the enantioselectivity, resulted in the formation of **3** ($R = \text{CH}_2\text{Ph}$) in 92 % yield with 93 % *ee* (*R*) after 8.5 h at 0 °C. On the basis of this information, the slight decrease of the enantiomeric excess observed in the reaction with **5** compared to that with **4b** can be accounted for by the intervention of heterochiral-**5** (Scheme 2), which is considered to be a pseudoenantiomer of heterochiral-**4b**, having led to the production of **3** ($R = \text{CH}_2\text{Ph}$) with the opposite *S* configuration.

The unique phenomenon discussed above provides a new, yet powerful strategy in the molecular design of chiral catalysts; that is, the requisite chirality can be served by the simple binaphthyl moiety and an additional structural requirement for fine-tuning of reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure (Figure 1); this certainly obviates the use of two chiral units and should be greatly appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. For instance, quaternary ammonium bromides possessing a sterically demanding substituent such as **4c** can be easily prepared, and the benzylation of **2** with **4c** as a phase-transfer catalyst gave **3** ($R = \text{CH}_2\text{Ph}$) in 95 % yield with 92 % *ee* (Table 1, entry 4). Moreover, the enantioselectivity was enhanced to 95 % *ee* when **4d** was used as a catalyst (Table 1,



Figure 1. New strategy for the molecular design of chiral phase-transfer catalysts.

entry 5) and, interestingly, use of aqueous CsOH as a base at a lower reaction temperature led to an increase of reactivity with similar enantioselectivity (Table 1, entry 6).^[8] The generality of the present system was demonstrated with other representative alkyl halides (Table 1, entries 7–9).

To obtain spectroscopic evidence for the expected conformational interconversion, the dynamic structural behavior of **4c** in solution was analyzed by a variable-temperature ¹H NMR study. Figure 2 shows the temperature dependence of the ¹H NMR signals (benzylic protons) of the quaternary ammonium bromide **4c** in [D₂]dichloromethane at low temperature. The peak broadening at 283–263 K and sharpening to two sets of four benzylic signals (nearly 1:1 ratio) at 243 K clearly indicates that there is a rapid equilibrium between two diastereomeric, homochiral and heterochiral conformations that arises from rotation about the biphenyl axis. The composition of the conformational structures depends on temperature and the existence ratio of the homochiral isomer was found to increase as the temperature lowered.^[8] This observation is a result of the positive enthalpy ($\Delta H^\circ = 5.74 \text{ kcal mol}^{-1}$) and the identical-signed large entropy ($\Delta S^\circ = 23.1 \text{ cal mol}^{-1} \text{ K}^{-1}$) for the conversion from homochiral to heterochiral conformation.^[9, 10]

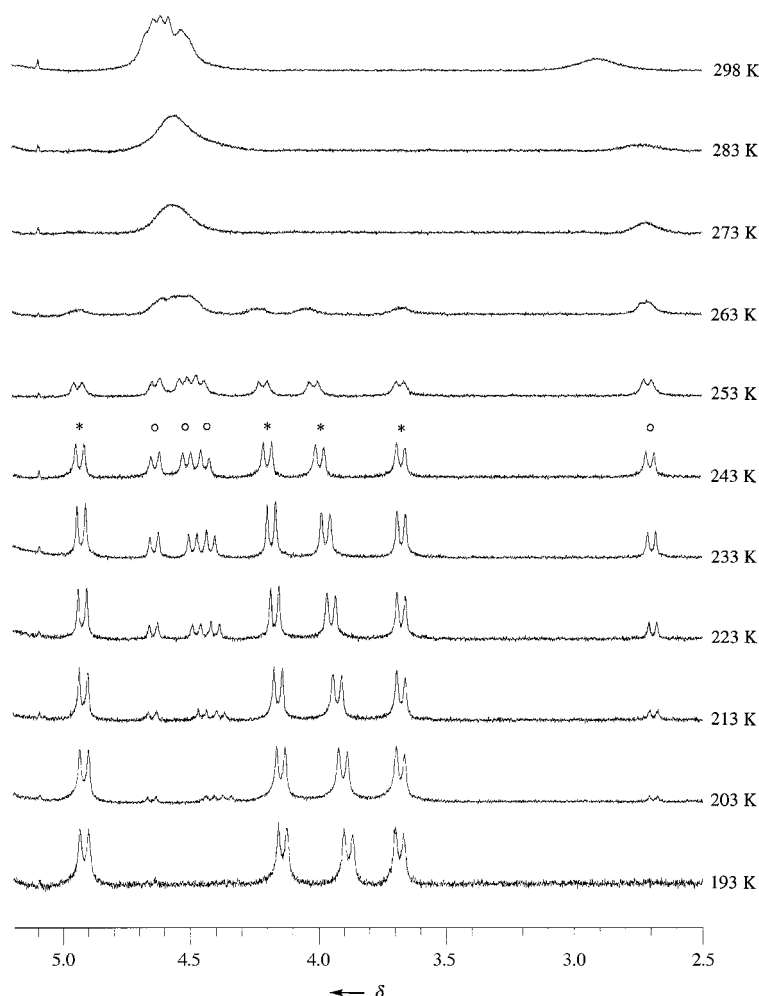


Figure 2. The temperature dependence of the ¹H NMR signals of the benzylic protons of homochiral (*) and heterochiral (o) conformers of **4c**.^[10]

In conclusion, we have described a new and simple strategy for the molecular design of chiral phase-transfer catalysts by introducing a conformationally flexible, chiral C_2 -symmetric quaternary ammonium bromide **4** and uncovering its characteristic feature. The representative phase-transfer alkylation of **2** was smoothly catalyzed by **4** in a highly enantioselective manner, which stems from the high chiral efficiency of a homochiral isomer rapidly equilibrating with a heterochiral one as verified by a variable-temperature ^1H NMR study. Our approach conceptually parallels the successful utilization of a flexible ligand to magnify the effect of the other chiral ligand through a coordinative interaction with the metal center,^[7] and should eventually offer a new dimension for asymmetric phase-transfer catalysis based on the design of the catalyst.

Experimental Section

Phase-transfer benzylation of **2** with catalyst **4d** (entry 6 in Table 1): Water (29.2 μL) was introduced to a 10-mL two-neck flask containing a Teflon-coated magnetic stirring bar and $\text{CsOH} \cdot \text{H}_2\text{O}$ (265 mg, 1.5 mmol) and the mixture was stirred under an argon atmosphere. Then, **4d** (5.8 mg, 0.005 mmol) and a solution of glycine *tert*-butyl ester benzophenone Schiff base **2** (148 mg, 0.5 mmol) in toluene (3 mL) were added and the mixture was cooled to -15°C . After 10 min of gentle stirring, benzyl bromide (73.6 μL , 0.6 mmol) was added dropwise and the reaction mixture was stirred vigorously for 16 h. The resulting mixture was poured into brine (25 mL) and extracted with CH_2Cl_2 (6 mL $\times$ 3). The organic layer was dried over Na_2SO_4 and concentrated. The residual oil was purified by column chromatography on silica gel (diethyl ether/hexane = 1:20 to 1:10 as eluant) to give the corresponding benzylation product **3** ($\text{R} = \text{CH}_2\text{Ph}$) (168 mg, 0.436 mmol; 87% yield, 94% *ee*) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol = 100:1, flow rate = 0.5 mL min^{-1} , retention time; 13.7 min (*R*) and 24.6 min (*S*)).

Received: November 26, 2001

Revised: February 18, 2002 [Z18273]

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A Model System Mimicking Glycosphingolipid Clusters to Quantify Carbohydrate Self-Interactions by Surface Plasmon Resonance**

María J. Hernáiz, Jesús M. de la Fuente, África G. Barrientos, and Soledad Penadés*

Dedicated to Professor Julio D. Martín on the occasion of his 60th birthday

Cell surface carbohydrates play a role in cell–cell adhesion and communication.^[1, 2] Several models for cell interactions based on carbohydrates have been proposed. In most of them, the carbohydrate binds to selectins, galectins, and other

[*] Dr. S. Penadés, M. J. Hernáiz, J. M. de la Fuente, Á. G. Barrientos
Grupo de Carbohidratos
Instituto de Investigaciones Químicas, CSIC
Isla de La Cartuja, Américo Vespucio s/n, 41092 Sevilla (Spain)
Fax: (+34) 95-4460-565
E-mail: penades@cica.es

[**] This work was supported by the DGES (PB960820) and EC (HPMF-1999-00241). M.J.H. thanks the Marie Curie program for a grant. J.M.F. thanks the MEC for a predoctoral fellowship. We thank Dr. L. Kremer and the Department of Immunology and Oncology of CNB for biosensor facilities, and Prof. M. Martín-Lomas for helpful advice and fruitful discussions.

carbohydrate-binding proteins.^[2] In 1989 Hakomori et al. proposed interactions between glycosphingolipid (GSL) microdomains as an initial step for adhesion and recognition.^[3] The process would consist of a highly specific low-affinity Ca^{2+} -dependent multivalent interaction between the carbohydrate moieties at the cell surface.^[4,5] The antigen Lewis^x (Le^x) is a trisaccharide ($\text{Gal}\beta(1\rightarrow4)[\text{Fuc}\alpha(1\rightarrow3)]\text{GlcNAc}$) carried by glycosphingolipids and poly-LacNAc ("embryoglycan"). Specific homotopic Le^x – Le^x interactions provide a possible basis for initial cell recognition in morula compaction and in embryonic carcinoma cells.^[6,7] Attempts to characterize and quantify this weak interaction in solution with monomeric Le^x ligands have failed.^[7,8]

Recently, we have prepared gold nanoclusters functionalized with self-assembled monolayers (SAMs) of biologically significant oligosaccharides as a new water-soluble three-dimensional (3D) polyvalent model system mimicking GSL clusters.^[9] With these gold glyconanoparticles we have demonstrated, by using transmission electron microscopy (TEM), the selective ability of the Le^x determinant for self-recognition in calcium-containing aqueous solution.^[9] This ability was also confirmed by an atomic force microscopy (AFM) study of adhesion forces between individual Le^x antigen molecules by using well-defined 2D-SAM surfaces.^[10]

Self-assembled monolayers of alkanethiols on gold are structurally well-organized substrates that provide excellent model surfaces for studies in biology.^[11,12] At the same time surface plasmon resonance (SPR) has been developed as an analytical method to investigate molecular recognition in carbohydrate–protein binding in real time.^[13] We now demonstrate that the combination of SAMs of alkanethiols on gold presenting carbohydrate epitopes as the substrate, gold glyconanoparticles as the analyte, and detection by SPR constitutes an excellent approach for studying and quantifying, in a well-defined system, the putative Ca^{2+} -mediated carbohydrate-to-carbohydrate interactions. The results now reported: a) provide, for the first time, a quantitative estimation of the kinetics for the self-interaction of the biologically important Le^x trisaccharide antigen; b) confirm the selective calcium dependency of this interaction; and c) illustrate, once more, the value of polyvalent presentation in the examination of weak interactions.^[14]

Two important reports have been published recently on the quantitative

estimation of carbohydrate interactions by SPR.^[15,16] In both of them the interacting oligosaccharides were attached to macromolecules (bovine serum albumin^[15] or polymers^[16]) that gave rise to a number of nonspecific interactions which hampered the study. In our system these unspecific interactions are minimized since the SAMs are prepared directly on the gold surface and we can control the nature of the ligand, its concentration, and its density at the gold surface.

The molecules used in this study are shown in Figure 1 A, and a schematic representation of a typical binding event (sensorgram) of our model system is given in Figure 1 B. Le^x trisaccharide and lactose neoglycolipids **1** and **3** were synthesized with a linker terminating with a thiol group, which enables the preparation of both polyvalent gold glyconanoparticles of Le^x (**1-Au**) and lactose (**3-Au**) as analytes and SAMs of **1** and **3** on the biosensor gold surfaces as substrates. The methyl glycosides **2** and **4** were also prepared as monovalent ligands.^[17] Sensor chips functionalized with SAMs of 11-thio-3,6,9-trioxaundecanol (**5**) and 11-thioundecanol (**6**)

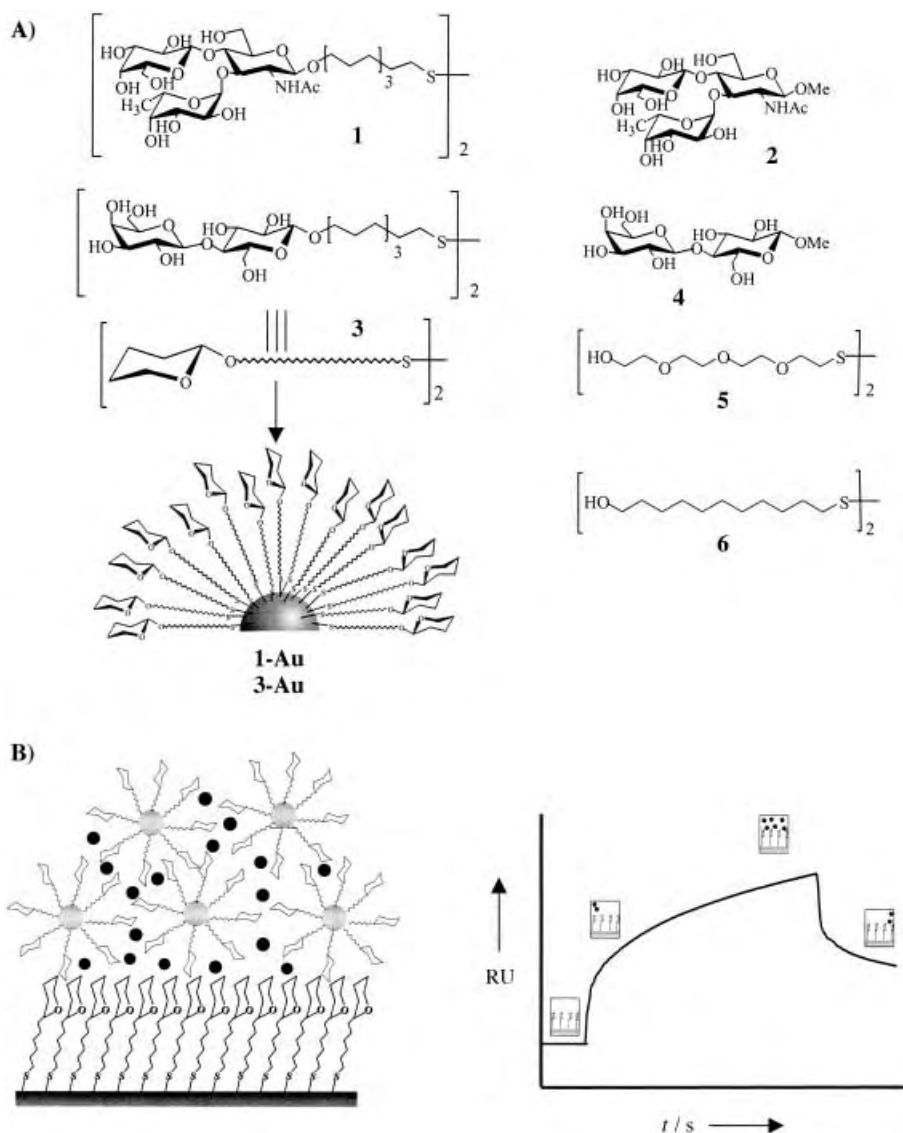


Figure 1. A) Structures of carbohydrate ligands used in this study; shaded hemisphere = gold nanoparticle. B) Schematic representation of our binding event strategy with a typical sensorgram; gray circles = gold nanoparticles, black circles = Ca^{2+} ions.

were used as control surfaces. Glyconanoparticles **1**-Au and **3**-Au have been prepared and characterized previously.^[9]

The SPR experiments were carried in a Biacore instrument (Biosensor AB, Uppsala) at 25 °C. A J1 biosensor chip (plain gold surface) was functionalized with neoglycolipids **1** (flow cell 1) and **3** (flow cell 2) at flow rate of 3 $\mu\text{L min}^{-1}$ until a constant SPR response (715 RU for **1** and 794 RU for **3**) was obtained (RU = response units). To cover possible gaps on the gold surface, the immobilization was continued by injection of an aqueous methanol solution (50 %) of **5** (2 mg mL⁻¹). In the third flow cell **5** was immobilized to remove any nonspecific interactions between the linker and carbohydrate ligands. The fourth flow cell of the sensor chip was treated only with buffer to serve as a second control. Alternatively, three different J1 sensor chips were functionalized by removing them from the plastic holder and soaking them in solutions of **1**, **3**, or **6** (2.5 mM) in ethanol. The results were similar to those obtained by the other protocol.

The binding of **1**-Au, **3**-Au, and the monovalent ligands **2** and **4** to SAMs of **1** and **3** were measured in Hepes buffer (Hepes = 2-[4-hydroxyethyl]piperazine-1-yl]ethanesulfonic acid) in the presence and absence of Ca²⁺ ions.^[18] Sensorgrams for the binding of **1**-Au, **3**-Au, and the corresponding monomeric ligands **2** and **4** to immobilized Le^x and *lacto*-neoglycolipids are shown in Figure 2. A plot of k_{obs} versus ligand concentration from the association phase yielded the rate constant k_{on} . At least six different concentrations of carbohydrate ligands were used. The dissociation rate constant k_{off} was obtained from the direct analysis of the dissociation phase of the sensorgrams. The rate constants k_{on} and k_{off} and the apparent affinity constants K_{d} are given in Table 1.

A slow association phase and a very gradual dissociation phase are shown in curves for the binding of Le^x nanoparticles (**1**-Au) to Le^x monolayers in the presence of calcium ions (Figure 2A). The binding is of high affinity, with a calculated K_{d} of $5.4 \times 10^{-7} \text{ M}$ (Table 1) and an RU value of 700 at a concentration of 1.8 μM . In contrast, binding of monovalent

Table 1. Kinetic data (k_{on} , k_{off} , and K_{d}) and energy of binding (ΔG) for monovalent and polyvalent ligands at 25 °C.^[a]

Monolayer surface	Carbohydrate ligand	k_{on} [M ⁻¹ s ⁻¹] ^[b]	k_{off} [s ⁻¹] ^[b]	K_{d} [M] ^[b]	$-\Delta G$ [kcal mol ⁻¹]
1	1 -Au	2.8×10^3	1.5×10^{-3}	5.4×10^{-7}	8.5
1	2	7.0×10	0.4	5.7×10^{-3}	3.0
1	3 -Au	5.0×10^2	0.4	80×10^{-3}	4.2
1	4	—[c]	—[c]	—[c]	—[c]
3	3 -Au	1.7×10^3	2.4×10^{-2}	150×10^{-3}	6.5
3	4	—[c]	—[c]	—[c]	—[c]
3	1 -Au	1.0×10^2	1.0×10^{-2}	10×10^{-3}	5.4
3	2	—[c]	—[c]	—[c]	—[c]

[a] 10 mM Hepes buffer (pH 7.4), 150 mM NaCl, 10 mM CaCl₂. The size of the statistical parameter χ^2 is <3 in all the fitting curves. [b] On the basis of the glyconanoparticle concentration. [c] After subtracting the data for nonspecific interactions from the gold and **5** surfaces (control lines) the signal was below 10 RU.

ligand **2** shows a very fast association and dissociation phase, which indicates a very weak interaction ($5.7 \times 10^{-3} \text{ M}$; Figure 2B). The ligands showed nonspecific interaction with the control lines (**5** and gold surface, data not shown). The data obtained suggest the importance of multivalent presentation of the ligand and how this contributes significantly to the binding affinity. No binding was observed in the absence of calcium ions. In comparison to the studies with Le^x glyconanoparticles, the binding of *lacto*-glyconanoparticles (**3**-Au) to lactose monolayers exhibits a rapid association phase but a slightly lower response (275 RU) and a very fast dissociation phase (Figure 2C). The K_{d} drops to $1.5 \times 10^{-5} \text{ M}$ which indicates that the affinity and strength of the binding decrease to the mM range for the lactose–lactose interaction (Table 1). No binding was observed for the monomeric ligand **4** either in the presence or absence of Ca²⁺ ions.

Crossed SPR experiments between immobilized Lewis X and *lacto*-nanoparticles or vice versa also gave affinity constants in the mM range (Table 1). Monovalent ligands **2** and **4** did not show any interaction in the crossed experiments. Similarly, the response observed for the interaction of the poly- (**1**-Au, **3**-Au) and monovalent (**2** and **4**) ligands with the immobilized monolayers of **5** and **6**, after subtracting background binding to the gold surface, was below the detection sensibility of the signal in the Biacore instrument (RU < 10). Thus, no selective interaction occurs between carbohydrate ligands and these surfaces.

These results indicate that the affinity of the Le^x antigen for self-recognition is in the μM range, whereas the lactose self-interaction and the heterotopic Le^x–*lacto* interaction show affinity constants in the mM range. The selectivity of Le^x nanoparticles for the Le^x monolayer is about 200 times higher ($\Delta\Delta G \sim 3 \text{ kcal mol}^{-1}$) than for the *lacto* monolayer and 30 times higher ($\Delta\Delta G \sim 2 \text{ kcal mol}^{-1}$) than that of the *lacto* nanoparticles for its self-assembled monolayers (Table 1). The binding affinity for Le^x self-recognition ($\Delta G \sim 8 \text{ kcal mol}^{-1}$) equals the

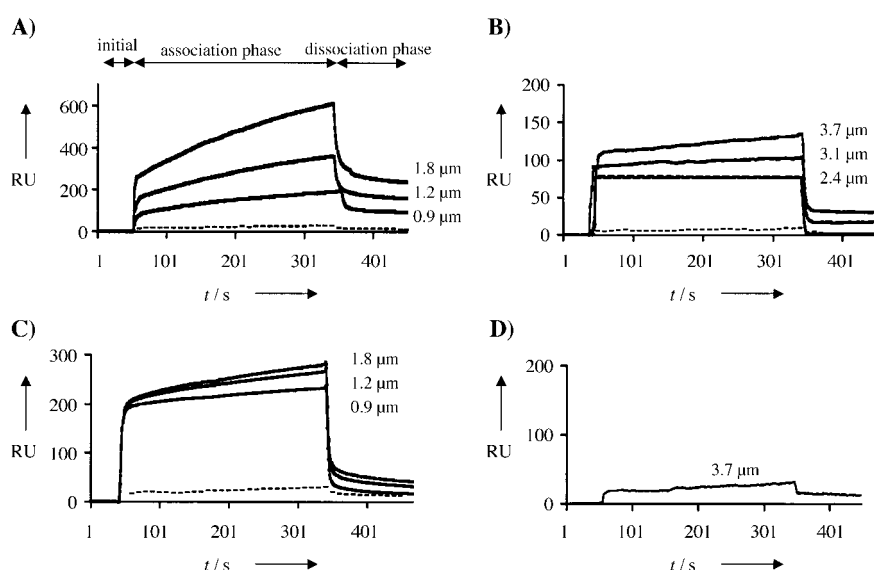


Figure 2. SPR sensorgrams for the interaction of: A) **1**-Au to SAMs of **1**; B) **2** to SAMs of **1**; C) **3**-Au to SAMs of **3**; D) **4** to SAMs of **3**, without (---) and with Ca²⁺ ions (—).

affinity determined for the heterotopic binding of polymeric Gg3 to GM3 monolayers,^[16] which is a model system mimicking the Gg3–GM3 interaction between lymphoma and melanoma cells.^[19] However, the selectivity found for the Ca²⁺-mediated Le^X–Le^X interaction related to the Le^X–*lacto* in our model system is about 3 kcal mol^{−1} higher than that found between Gg3–GM3 and Gg3–*lacto* interactions ($\Delta\Delta G < 1$ kcal mol^{−1}) in the monolayer–polymer system.^[16]

The selective Le^X–Le^X recognition in our model system is Ca²⁺ dependent. In the absence of Ca²⁺ ions, Le^X nanoparticles bind to all functionalized surfaces as they do to the bare gold surface (Figure 2A). The selective role of Ca²⁺ ions is also shown in the apparent rate of dissociation of Le^X nanoparticles–Le^X surface complex (Figure 2A). Addition of 10 mM ethylenediamine tetraacetate (EDTA) solution to the buffer was necessary to remove the Le^X surface associate complex, whereas in the case of the *lacto*–*lacto* complex, buffer solution was sufficient to regenerate the *lacto*-functionalized surface (Figure 2C). These and our previous results from transmission electron microscopy (TEM)^[9] indicate that Ca²⁺ ions are necessary for selective Le^X self-recognition and agree also with the early observation of Ca²⁺-dependent aggregation of Le^X-coated beads.^[7] In contrast, the presence of calcium ions does not contribute significantly to the adhesion forces in the atomic force microscopy (AFM) experiment.^[10] This selective calcium dependency may also explain the differences in binding behavior between the monomeric ligands Le^X **2** ($K_d = 5.7$ mM) and lactoside **4** (Figure 2B and D). The response observed for **2** (130 RU), despite its low molecular weight, may be due to Ca²⁺-mediated higher molecular aggregates that allow the detection of the interaction on the SPR experiment. This may be also the reason that the apparent affinity of monomeric Le^X (**2**) for immobilized Le^X monolayers, as measured by SPR, is two orders of magnitude higher than that obtained for the binding of **2** to Le^X-containing liposomes ($K_d = 0.3$ M), as determined by NMR spectroscopy.^[20]

The elusive nature of carbohydrate–carbohydrate interactions, which has made their identification and study very difficult, has been our focus since 1990.^[21] We provide here the first quantitative kinetic data for Le^X self-recognition and direct evidence of its Ca²⁺ dependency. The cooperative character of this polyvalent interaction has been proved as well ($\beta = 10^4$).^[14] Low multivalency may be the reason that Le^X self-recognition could not be observed in other model systems.^[15] In addition, incorrect presentation of the oligosaccharide epitopes may be responsible for the weak interaction observed in liposome systems.^[20, 22] The data here reported, together with our previous results,^[9] clearly support the proposal that Le^X carbohydrate self-interaction can be a relevant mechanism for cell adhesion and recognition.^[6] Gold glyconanoparticles and SAMs presenting carbohydrate epitopes constitute an excellent biomimetic model of carbohydrate presentation at the cell surface. These tools together with the application of new analytical techniques (SPR and AFM) are allowing us to unravel the molecular basis of other carbohydrate-mediated interactions.

Received: December 6, 2001 [Z18337]

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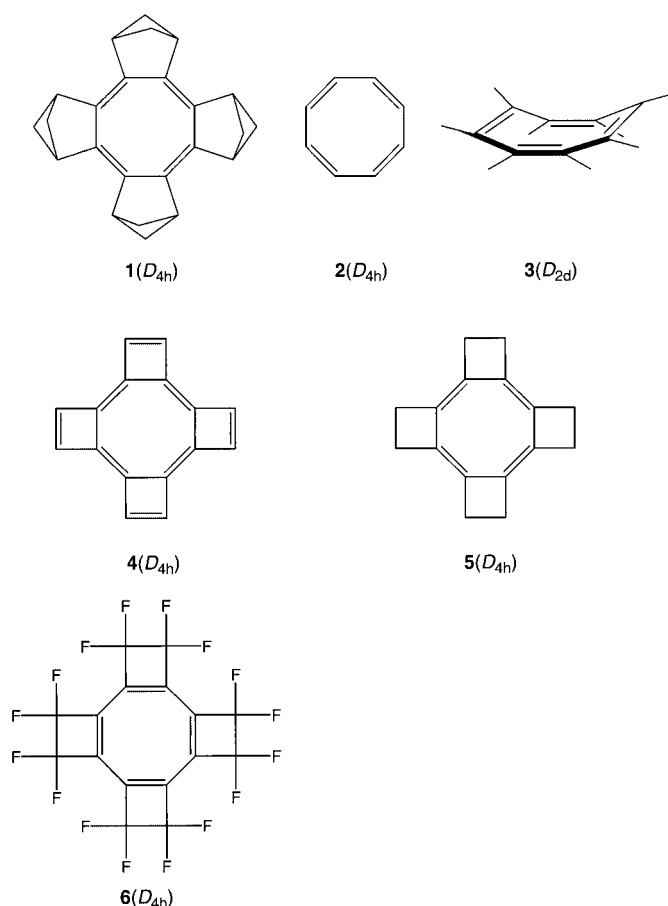
Paratropic Delocalized Ring Currents in Flattened Cyclooctatetraene Systems with Bond Alternation**

Patrick W. Fowler, Remco W. A. Havenith, Leonardus W. Jenneskens,* Alessandro Soncini, and Erich Steiner

The classical Hückel and London theories of monocyclic π systems lead to an expectation of *diatropic* and *paratropic* ring currents in cycles with $4n + 2$ and $4n$ π electrons, respectively.^[1] In practice, benzene famously bears out this expectation,^[2, 3] but the 8π -antiaromatic cyclooctatetraene (COT) distorts to achieve a nonplanar closed-shell configuration with localized double bonds,^[4] and behaves chemically as a conjugated alkene.^[5]

Synthetic chemists have shown an interest in using annulation with rigid bridges to impose geometric constraints to localize the electronic structure of benzene^[6–9] and, conversely, to impose a delocalized structure on COT.^[10, 11] The recent synthesis of a stable annulated cyclooctatetraene, tetrakis(bicyclo[2.1.1]hexeno)cyclooctatetraene (**1**, Scheme 1),^[11] in which the eight-membered ring is confined to the plane but retains strong bond alternation (X-ray average; $\Delta R(\mathbf{1}) = 0.169 \text{ \AA}^{[11]}$), raises the question of whether this molecule will now follow the original Hückel–London expectation and, in spite of its bond alternation,^[12] support a delocalized paratropic ring current. The positive nucleus-independent chemical shift (NICS)^[13] value of $\delta = 10.6 \text{ ppm}$ calculated for the octagonal ring, though much smaller than that for planar COT (**2**(D_{4h}) $\delta = 27.2 \text{ ppm}$),^[11] is one indication of such a current. Unfortunately, **1** does not have the protons attached to its planar COT ring that would allow direct diagnosis by ^1H NMR spectroscopy, whilst its bridgehead protons lie outside the shielding/deshielding cone of the central ring. (In fact, the remoteness of the bridgehead protons explains the small size of the observed shift of $\delta = 0.18 \text{ ppm}$,^[6, 11] despite reversal of ring currents, between **1** and tris(bicyclo[2.1.1]hexeno)benzene; the ^1H NMR chemical shifts of bridgehead protons are similar in several bicyclo[2.1.1]hexeno-clamped derivatives of benzene and COT.^[6, 11, 14, 15]).

Here we use computed current–density maps to answer the question of whether **1** supports a delocalized paratropic ring current. Consideration of the maps leads to a general analysis of the factors that decide when a constrained ring will carry a



Scheme 1. Molecules under study.

ring current. Comparisons of currents in **1**(D_{4h}) with those in planar COT (**2**(D_{4h})), COT in its tub-shaped equilibrium geometry (**3**(D_{2d})) and COT moieties in hypothetical tetrakis(cyclobutadieno)- (**4**(D_{4h})) and tetrakis(cyclobuteno)cyclooctatetraene (**5**(D_{4h}), Scheme 1), will show that the choice of bridges used to effect clamping of COT into the plane determines whether or not a ring current exists.

Modern, distributed-origin, coupled Hartree–Fock methods such as the continuous transformation of origin of current density (CTOCD) method^[16–19] are particularly suited for the visualization and interpretation of ring currents^[20] (see Computational Section). Maps are shown in Figure 1 for the computed π -only and total ($\sigma + \pi$) current densities in **1**(D_{4h}). A strong, central paratropic ring current is evident in both

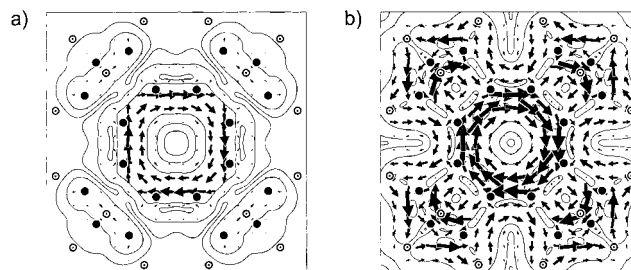


Figure 1. Maps of current density in tetrakis(bicyclo[2.1.1]hexeno)cyclooctatetraene (**1**): a) π -only, b) total ($\sigma + \pi$) current (● carbon, ○ hydrogen; nuclear positions projected in the plotting plane).

[*] Prof. Dr. L. W. Jenneskens
Debye Institute, Department of Physical Organic Chemistry
Utrecht University
Padualaan 8, 3584 CH Utrecht (The Netherlands)
Fax: (+31) 30-253-4533
E-mail: jennesk@chem.uu.nl

Prof. Dr. P. W. Fowler, Dr. R. W. A. Havenith, A. Soncini,
Dr. E. Steiner
School of Chemistry, University of Exeter
Stocker Road, Exeter EX4 4QD (UK)
Fax: (+44) 1392-26-3434

[**] We are grateful for an International Author Travel Grant from the Royal Society of Chemistry (Grant 0012289) to L.W.J. and thank the European Union TMR and Marie-Curie schemes (contracts FMRX-CT097-0192 (Biofullerenes, R.W.A.H.) and HPMT-CT-2000-00016 (A.S.))

maps. The π contribution shows some variation in strength between alternate long and short bonds, which tends to equalize on inclusion of σ effects. Apart from the main paratropic ring current, some extraneous features arise in the total ($\sigma + \pi$) map where the plotting plane cuts through the bridge bonds of the four bicyclo[2.1.1]hexeno units. However, the constrained COT subunit in this new molecule does indeed sustain the classical Hückel π current expected from its antiaromatic electron count. The question is whether this observation is a simple consequence of the enforced planarity of COT in **1**.

The answer is provided by the planar form of COT itself. On optimization in D_{4h} symmetry, the resulting closed-shell COT structure (**2** (D_{4h})), which is the transition state for tub-to-tub inversion,^[21] exhibits bond alternation similar to that in the subunit of the stable molecule **1** (6-31G**): $\Delta R(\mathbf{1}) = 0.184 \text{ \AA}$, $\Delta R(\mathbf{2}) = 0.153 \text{ \AA}$. Planar COT (**2**) also displays the classical intense paratropic ring current expected for an antiaromatic π system (Figure 2a), associated here with the splitting into b_{2u} HOMO and b_{1u} LUMO in D_{4h} of the degenerate e_{2u} HOMO of the D_{8h} open-shell.^[22] The reduced ring current of the stable molecule **1** is consistent with its larger HOMO–LUMO gap (**1**: 9.4 eV versus **2**: 8.5 eV).

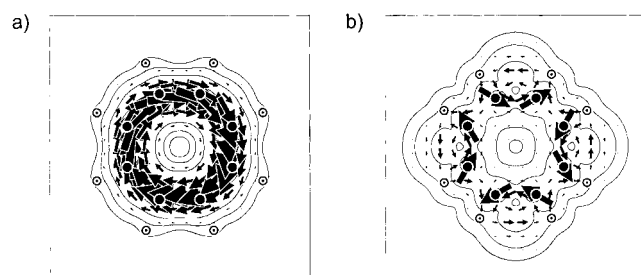


Figure 2. Maps of π -current density in a) planar COT (**2**), b) tub-shaped COT (**3**) (● carbon, ○ hydrogen; in (a) nuclear positions projected in the plotting plane. In (b) the median plane was used as the plotting plane).

Relaxation of COT to its tub-shaped equilibrium geometry **3** (D_{2d}) has little effect on the bond alternation (6-31G**): $\Delta R(\mathbf{3}) = 0.155 \text{ \AA}$ but destroys the delocalized ring current, as Figure 2b shows. Long and short bond lengths are similar for all three COT structures (**1**, X-ray averages 1.331(1)/1.500(1) $\text{\AA}$; 6-31G** values: **1** (D_{4h}), 1.323/1.507 $\text{\AA}$, **2** (D_{4h}), 1.326/1.479 $\text{\AA}$, **3** (D_{2d}), 1.323/1.478 $\text{\AA}$). The π -only map for **3** drawn in the median plane of the molecule shows localized circulations from the four double bonds, two above and two below the plotting plane. From this comparison of **2** and **3**, the importance of planarity is clear, notwithstanding previous literature statements,^[12] but planarity alone is insufficient to ensure presence of a current, as the next example shows. In **4** (D_{4h} ; see Scheme 1) the COT subunit is again clamped in the plane, in this case by annelation with rigid cyclobutadieno rings. In contrast to **1**, the π and total ($\sigma + \pi$) maps for **4** (Figure 3) show the typical signature of localized double bonds. No paratropic π ring current is discernible in the COT unit of **4**, though the unsaturated four-membered cycles themselves support central (σ) paratropic contributions.

This quenching of the paratropic COT π current in **4** arises specifically from the conjugation of the clamping group with

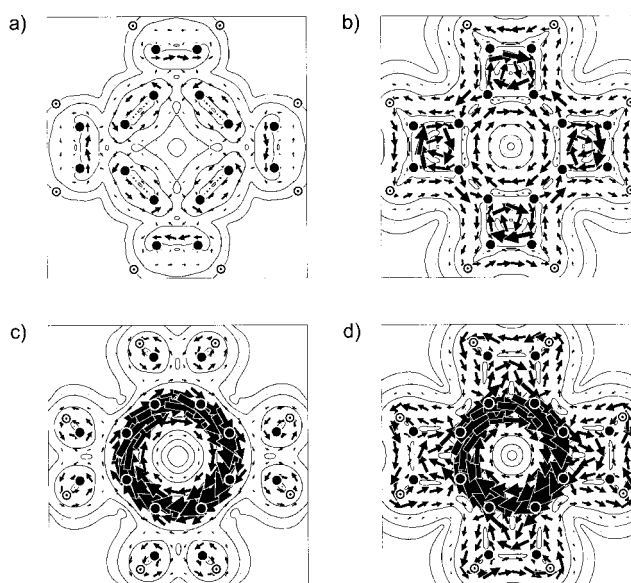


Figure 3. Maps of current density in tetrakis(cyclobutadieno)cyclooctatetraene (**4**) and tetrakis(cyclobuteno)cyclooctatetraene (**5**): a) π -only current in **4**, b) total ($\sigma + \pi$) current in **4**, c) π -only current in **5**, and d) total ($\sigma + \pi$) current in **5** (● carbon, ○ hydrogen; nuclear positions projected in the plotting plane).

the central ring. When the external π bonds of **4** are hydrogenated, to give the planar tetrakis(cyclobuteno) derivative **5** (D_{4h}), the COT paratropic current is restored (Figure 3c). The difference in current maps between **1**, **5** on the one hand and **4** on the other is evidently not a consequence of differences in bond alternation, (6-31G**): $\Delta R(\mathbf{4}) = 1.501 - 1.317 = 0.184 \text{ \AA}$, $\Delta R(\mathbf{5}) = 1.491 - 1.317 = 0.174 \text{ \AA}$. The explanation of the switch from localized to delocalized behavior lies instead in the difference between the π electronic structures of the 16-electron conjugated system in **4** and the eight-electron COT system in **1**, **2**, and **5**. As noted above, the planar COT ring has a b_{2u} HOMO and b_{1u} LUMO (Figure 4), and these are also HOMO and LUMO in **1** and **5**. The $b_{2u} \rightarrow b_{1u}$ occupied-to-virtual transition has the symmetry of a rotation about the magnetic field direction, and therefore produces a paratropic contribution.^[22] This low-energy transition dominates the total π ring current and determines its paratropic sense. In **4** however, the interaction of the central COT π system (bonding orbitals a_{2u} , e_g , b_{2u} ; antibonding b_{1u} , e_g , a_{1u}) with the four outer π bonds (bonding combinations a_{2u} , e_g , b_{1u} ; antibonding b_{2u} , e_g , a_{1u}) pushes the occupied b_{2u} orbital down, below $2a_{2u}$ (HOMO–1) and $2e_g$ (HOMO), and pushes the empty b_{1u} orbital up, above the $3e_g$ (LUMO) and $1a_{1u}$ (LUMO+1) (Figure 4). The large paratropic $1b_{2u}$ orbital contribution is thereby suppressed and replaced by a mixture of weaker contributions ($2e_g \rightarrow 3e_g$ (paratropic), $2a_{2u} \rightarrow 3e_g$ (diatropic), $1b_{2u} \rightarrow 3e_g$ (diatropic)), which sum to localized diamagnetic circulations in the eight π bonds of **4**. In the language of reference [22], two-electron paramagnetism in **1**, **2**, and **5** has been replaced by eight-electron diamagnetism in **4**. This is a direct consequence of π – π interaction between COT and the clamping groups (see also references [23, 24]; if the *exo* single bonds of **4** are artificially stretched to 2 $\text{\AA}$, for example, the central paratropic COT current reappears).

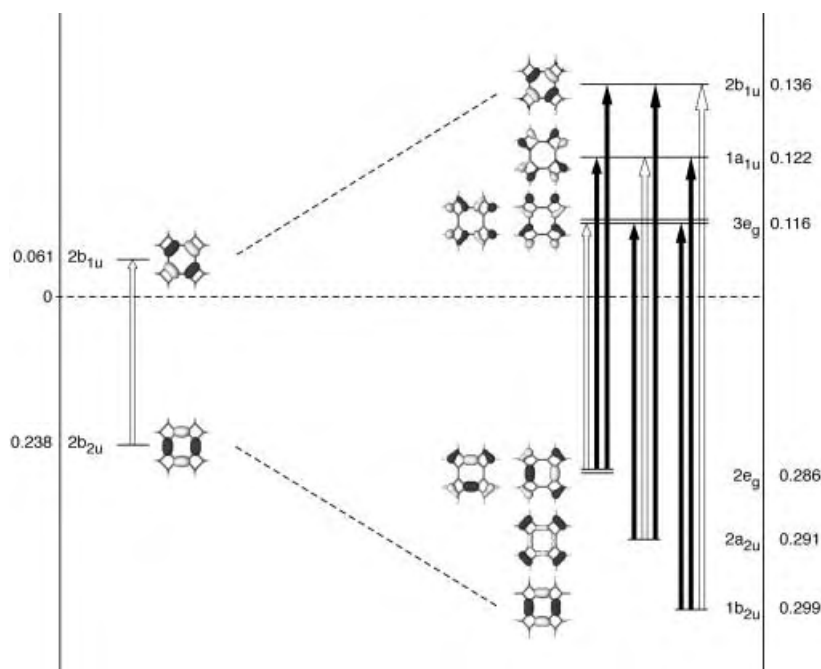


Figure 4. Three-dimensional contour maps of the HOMOs and LUMOs of **4** (right) and **5** (left), indicating their energies (Hartree) and symmetries. Black arrows represent translational transitions and white arrows rotational transitions from occupied levels.^[22] The π molecular orbitals of **1** and **2** are similar to those of **5**.

The orbital picture also gives a ready explanation of the properties of other species such as perfluorinated tetrakis(cyclobuteno)cyclooctatetraene (**6** (D_{4h}), Scheme 1).^[25] Replacement of H by F in **5** stabilizes the *endo* tautomer **6**,^[12] but as this corresponds to a simple switch of HOMO and LUMO symmetries, the paratropic ring current should be retained. Explicit CTOCD-DZ calculations of current maps (not shown) confirm this expectation: **6** has indeed a strong central paratropic π current of similar intensity to that in **5**.

The series of calculations described here show that when COT is made planar, its magnetic response is essentially independent of the degree of bond alternation. A paratropic π ring current is compatible with clamping by groups that exert a purely geometrical effect. The crucial factor in the survival of the ring current is the rotationally allowed COT HOMO–LUMO transition; when interaction with the π system of an unsaturated clamping group opens up the gap between the b_{2u} and b_{1u} orbitals, the ring current is destroyed. In this context, the bicyclo[2.1.1]hexeno and cyclobuteno clamping groups are passive spectators, whereas the cyclobutadieno clamp actively suppresses the antiaromatic central current. The bicyclo[2.2.2]octene group^[10] is also a spectator in this sense to a diamagnetic current in COT^{2–}.

A parallel distinction in localization of central current is expected to apply to the equivalent derivatives of benzene.^[6–9, 26]

Computational Section

Methods: The magnetic properties of all molecules were computed by using distributed-origin methods,^[16, 17] at the coupled Hartree–Fock level,^[18, 19] with the SYSMO program.^[27] For the current–density maps, well-converged results are given by the DZ (diamagnetic zero) variant of the CTOCD (continuous transformation of origin of current density)

method, where the current density at any point in space is calculated with that point as origin.^[16–19] The method has the usual advantages of distributed-origin approaches: superior convergence with basis size and physically realistic current maps with modest basis sets (here 6–31G**). Optimized geometries, confirmed as minima (**1**, **3–6**) or in one case a transition state (**2**: one imaginary frequency), were computed in the same basis.

For all but **3** (see legend to Figure 2), current densities induced by a unit magnetic field acting along the principal axis are plotted in a plane 1 a_0 above that of the central ring (that is, close to the maximum π density and with current essentially parallel to the molecular plane, as shown previously^[28]), the plotting area is $16 \times 16 a_0^2$, the contours denote the modulus of the current density, and the vectors represent in-plane projections of current. In all plots, diamagnetic circulation is shown anticlockwise and paramagnetic circulation clockwise.

Received: June 11, 2001
Revised: February 18, 2002 [Z17268]

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A Three-Dimensional Homometallic Molecular Ferrimagnet**

Sanjit Konar, Partha Sarathi Mukherjee, Ennio Zangrando, Francesc Lloret,* and Nirmalendu Ray Chaudhuri*

Multidimensional molecular-based magnets are the focus of considerable current research effort from both fundamental and device-related perspectives.^[1] Two- or three-dimensional (2-D, 3-D) homometallic magnetic systems can behave as ferromagnetic, antiferromagnetic, or as metamagnetic materials depending on the nature of the spin coupling.^[1b, 2] However, an example of a 3-D homometallic system with ferrimagnetic behavior has not yet been reported because the conditions for the noncompensation of the individual spin moments are difficult to achieve in these systems. In this communication we report the synthesis, crystal structure, and magnetic behavior of a 3-D homometallic ferrimagnet that orders magnetically at 6 K. To the best of our knowledge, this is the first 3-D homometallic molecular ferrimagnet.

Hydrothermal treatment of $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with disodium fumarate ($\text{Na}_2(\text{CO}_2\text{CH}=\text{CHCO}_2)$; $\text{Na}_2(\text{fum})$) in water at 170°C leads to the formation of the complex $[\text{Ni}_3(\text{fum})_2(\mu_3\text{-OH})_2(\text{H}_2\text{O})_4]_n \cdot (2\text{H}_2\text{O})_n$ **1**. The X-ray analysis shows a 3-D structure^[3] formed by chains of fused Ni^{II} octahedral units. These chains, in which all the metal atoms are coplanar, include two crystallographically independent ions: A symmetry related pair $\text{Ni}(1)$ and $\text{Ni}(1')$ separated by $3.017(1)$ Å that alternates with $\text{Ni}(2)$, located on a center of symmetry. The $\text{Ni}(1)$ – $\text{Ni}(2)$ and $\text{Ni}(1')$ – $\text{Ni}(2)$ distances are $3.661(1)$ and $3.557(1)$ Å, thus forming a figure close to an isosceles triangle. The three metal atoms share an edge of their octahedron, being capped by the hydroxyl oxygen $\text{O}(5)$, alternatively above and below the chain but slightly displaced by 0.55 Å (Figure 1). The fumarate carboxylate groups bridge the longest edges of the metal triangle, completing the coordination sphere of $\text{Ni}(2)$, whereas the hexacoordination about

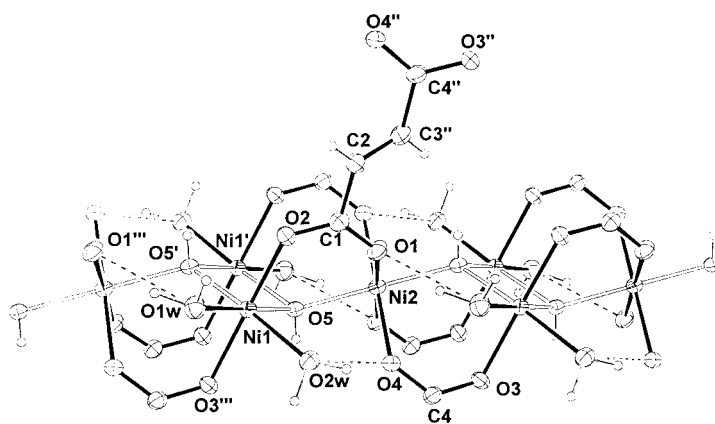


Figure 1. ORTEP plot (40% thermal ellipsoids) of the metal chain and atomic numbering scheme for **1**. Open bonds indicate Ni–OH connections; only a single complete fumarate anion is shown for the sake of clarity. Coordination bond lengths and intermetallic distances [Å]: $\text{Ni}(1)$ – $\text{Ni}(1')$ $3.017(1)$, $\text{Ni}(1)$ – $\text{Ni}(2)$ $3.661(1)$, $\text{Ni}(1')$ – $\text{Ni}(2)$ $3.557(1)$, $\text{Ni}(1)$ – $\text{O}(1\text{w})$ $2.101(3)$, $\text{Ni}(1)$ – $\text{O}(2\text{w})$ $2.107(3)$, $\text{Ni}(1)$ – $\text{O}(2)$ $2.039(3)$, $\text{Ni}(1)$ – $\text{O}(3)$ $2.066(3)$, $\text{Ni}(1)$ – $\text{O}(5)$ $2.079(3)$, $\text{Ni}(1)$ – $\text{O}(5')$ $2.038(3)$, $\text{Ni}(2)$ – $\text{O}(1)$ $2.085(3)$, $\text{Ni}(2)$ – $\text{O}(4)$ $2.074(3)$, $\text{Ni}(2)$ – $\text{O}(5)$ $2.068(3)$. Symmetry operations: $(x, y, z)' = (-x + 1, -y + 2, -z + 1)$; $(x, y, z)'' = (x, -y + 3/2, z + 1/2)$; $(x, y, z)''' = (x + 1, y, z)$.

$\text{Ni}(1)$ is achieved through the oxygen atoms of two water molecules, $\text{Ow}(1)$ and $\text{Ow}(2)$. The Ni–O distances with fumarate oxygen atoms and hydroxo ligand are all comparable and range from $2.039(3)$ to $2.085(3)$ Å, while those involving the water molecules are slightly longer ($\text{Ni}(1)$ – $\text{O}(1\text{w})$ $2.101(3)$ and $\text{Ni}(1)$ – $\text{O}(2\text{w})$ $2.107(3)$ Å). The O–Ni–O *cis* angles lie in the range from $83.2(1)$ to $96.8(1)^\circ$, namely with a deviation of $\pm 7^\circ$ from the ideal 90° value required for a purely octahedral coordination geometry. The dicarboxylate anions, acting as a bridging bis-bidentate ligand, diverge from the chain and connect to metal centers of an adjacent chain, thereby leading to a 3-D framework where the shortest Ni–Ni interchain distance is 8.140 Å. Figure 2 shows a view of the 3D framework with channels occupied by crystallization

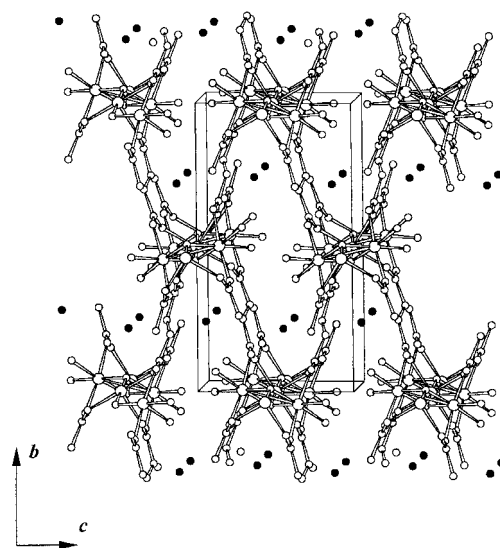


Figure 2. Packing view along axis *a* showing the 3-D structure with crystallization water molecules (oxygen atoms as shaded spheres) located in the framework.

[*] Prof. N. R. Chaudhuri, S. Konar
Department of Inorganic Chemistry
Indian Association for the Cultivation of Science
Kolkata 700032 (India)
Fax: (+91)33-473-2805
E-mail: icnrc@mahendra.iacs.res.in

Prof. F. Lloret
Departament de Química Inorgànica
Universitat de València
46100 Burjassot (Spain)
Fax: (+34)6-386-4322
E-mail: Francisco.Lloret@uv.es

P. S. Mukherjee
Department of Chemistry
Kalna College
Kalna 713409 (India)

Prof. E. Zangrando
Dipartimento di Scienze Chimiche
University of Trieste
34127 Trieste (Italy)

[**] The authors are grateful to the Council of Scientific and Industrial Research (New Delhi) and Spanish Ministry of Science and Technology through project BQU2001-2928 for financial support.

water molecules. It is worthwhile to note that the coordinated water molecules make intrachain (O(1w)–O(1) 2.781, O(2w)–O(4) 2.810 Å; see Figure 1) and interchain hydrogen bonds (O(1w)–O(2w) 2.847 Å) that reinforce the overall structure. Finally, a solvent water molecule, O(3w), accommodated in the channels (Figure 2) is bound to the framework through O(2) (2.892 Å) and O(3) (2.712 Å). A few structurally characterized compounds containing Ni^{II} chains with di- and polyfunctional ligands have been reported so far. Metal chain complexes with oligopyridylamino ligands represent a remarkable example of a metal wire^[4] with intermetallic distances in the range 2.20–2.38 Å. Structural features of the present metal chain seem more appropriately compared with a nickel chloride sequence,^[5] formed by pentameric oligomers (Ni–Ni distances of about 3.0 Å) linked through di-μ-chloro bridges (Ni–Ni 3.4 Å), where the intermetallic distances are comparable to those reported here. However, the present structure, of infinite -(Ni)₂-Ni- units capped by a μ₃-hydroxo ligand and bridged by dicarboxylate fumarate anions, represents an unique example of a 3-D network.

The magnetic behavior^[6] of the title complex **1** is shown in Figure 3 in the form of $\chi_M T$ versus T plot (χ_M is the magnetic susceptibility per three Ni^{II} ions). This curve shows that at

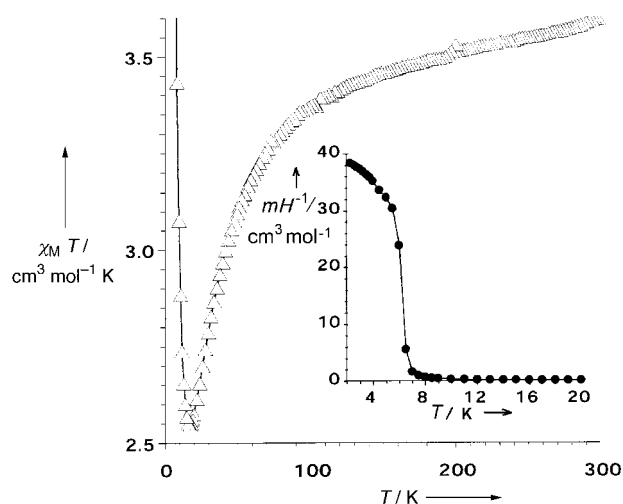


Figure 3. Plot of $\chi_M T$ versus T for **1**. Inset: Field-cooled magnetization curve (under an applied magnetic field $H = 100$ G) showing ferromagnetic order at 6 K.

room temperature the $\chi_M T$ value ($3.5 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$) corresponds to three magnetically isolated Ni^{II} ions and when the temperature decreases the $\chi_M T$ values decrease; a minimum ($2.5 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$) is observed at 17 K. Below this minimum, $\chi_M T$ rapidly increases and reaches a very high value before becoming strongly field dependent at around 6 K ($\chi_M T = 170 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ at 5.5 K for $H = 100$ G). This curve is characteristic of ferrimagnetic behavior. The inset of Figure 3 shows the field-cooled magnetization and reveals spontaneous magnetization at 6 K. This critical temperature is also confirmed by an ac-susceptibility measurement. Finally, the magnetization curve, which is shown in Figure 4, exhibits a saturation value about 2.2 BM and a hysteresis loop with a critical field of 65 G and remnant magnetization of 0.55 BM

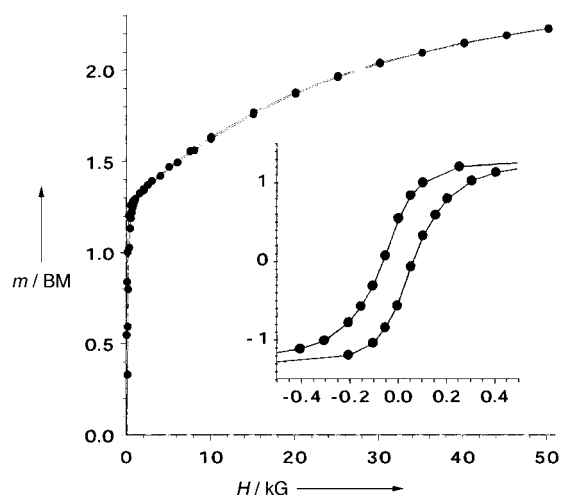


Figure 4. Magnetization curve for **1** at 2 K. Inset: Hysteresis loop at 2 K with decreasing H first.

(see Figure 4 inset). All these data indicate that **1** behaves as a magnet with a spontaneous magnetization below 6 K.

In the structure we have a chain with hydroxo and carboxylate bridges. The hydroxo bridge has Ni–O(H)–Ni angles lying in a range for which ferromagnetic coupling between two Ni^{II} centers has been observed,^[7] and a $S = 2$ ground spin state for this fragment is expected at a low temperature. The single hydroxo (open angle) and carboxylate bridges give antiferromagnetic interaction between the Ni(2) atom ($S = 1$) and the ferromagnetic fragment ($S = 2$), leading to a ferrimagnetic chain system with alternating $S = 2$ and $S = 1$ spin values (Figure 5). Individual ferrimagnetic chains interact with adjacent chains in a ferromagnetic fashion through the fumarate skeleton to yield a ferromagnetic compound below 6 K. The saturation value (2.2 BM) in

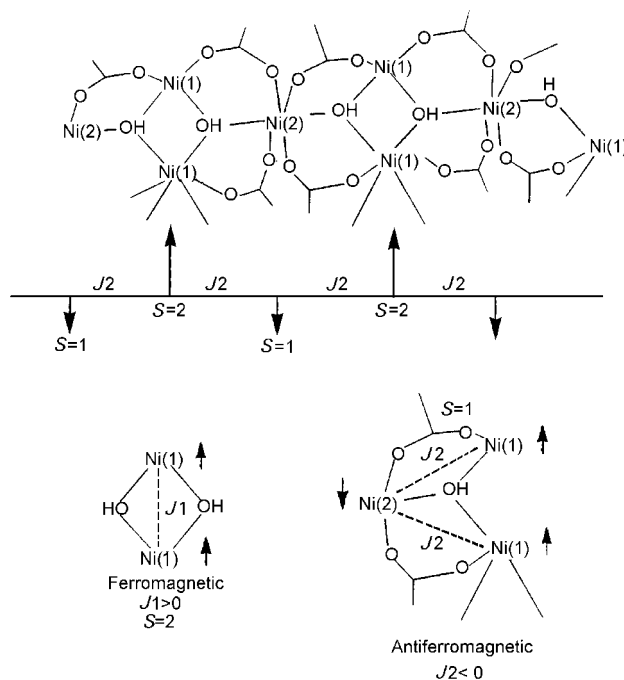


Figure 5. Spin states of the Ni^{II} chain in the ground state overlaid onto the molecular structure. The alternating spin states produce a ferrimagnetic chain system.

the magnetization curve (Figure 4) is in agreement with the magnetic coupling scheme proposed above, that is, antiferromagnetic coupling between $S=1$ and $S=2$ leads to a triplet ground spin state with $g=2.2$. These features rule out the possibility of magnetic ordering through spin canting or a helical ferromagnet. Further magnetic properties of this unique homometallic system are under investigation.

Experimental Section

1: In a typical synthesis, $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (1 mmol) was heated with $\text{Na}_2(\text{fum})$ (1 mmol) in water (15 mL) at 170°C for 24 h in a teflon-lined steel vessel. Overnight cooling of the vessel results in a microcrystalline green solid along with single crystals (65% yield) suitable for X-ray diffraction. Elemental analysis (%): calcd (found): C 17.57 (17.66), H 3.29 (3.38).

Received: October 2, 2001 [Z18010]

Revised: February 12, 2002

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- [3] Crystal data: $\text{C}_8\text{H}_{18}\text{Ni}_3\text{O}_{16}$ (**1**) $M_r=546.35$, monoclinic, space group $P2_1/c$, $a=6.558(3)$, $b=8.128(3)$, $c=15.506(4)$ Å, $\beta=96.36(3)^\circ$, $V=821.4(5)$ Å³, $Z=2$, $\rho_{\text{calcd}}=2.209$ g cm⁻³, $\mu=3.490$ mm⁻¹ ($\text{MoK}\alpha$), $F(000)=556$. θ range for data collection $4.01\text{--}30.15^\circ$, final $R=0.0508$, $wR2=0.1383$, $S=1.141$ for 146 parameters and 3606 reflections, 2216 unique [$R(\text{int})=0.0455$], of which 1866 with $I>2\sigma(I)$, max. positive and negative peaks in ΔF map 0.906 and -0.926 e Å⁻³. The data set was collected on a Nonius DIP-1030H system equipped with $\text{MoK}\alpha$ radiation ($\lambda=0.71073$ Å) at room temperature. A total of 30 frames were collected, each with a rotation of 6° about φ and an exposure time of 12 min over a half of reciprocal space; the detector is 80 mm from the crystal. Data reduction and cell refinement was carried out using the program MOSFLM.^[8] The structure was solved by Patterson and Fourier analyses and refined by the full-matrix least-squares method based on F^2 using SHELX 97^[9] to SHELX 86. All the calculations were performed using the WinGX System (Ver. 1.64).^[10] CCDC 171598 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via 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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Arene – Perfluoroarene Interactions as Physical Cross-Links for Hydrogel Formation**

Andreas F. M. Kilbinger and Robert H. Grubbs*

In 1960 Patrick and Prosser discovered that hexafluorobenzene (HFB, m.p. = 5.0°C) and benzene (m.p. = 5.4°C), both liquids at room temperature, form a 1:1 solid complex with a melting point of 23.7°C when mixed together.^[1] Extensive X-ray crystallographic studies by Dahl showed that a wide variety of aromatics^[2] form such 1:1 cocrystals with HFB, all showing alternating columnar face-to-face stacking. The packing behavior was explained theoretically to arise from electrostatic interactions between the two partners with the quadrupolar moment of HFB being complementary to that of benzene or its hydrocarbon derivatives.^[3, 4] The binding energy between the two aromatic rings (benzene – HFB) was computed to be 3.7 kcal mol⁻¹.^[5] Similar stacking motifs have been observed for several other cocrystals of perfluorinated aromatic compounds with their non-fluorinated analogues.^[6–8] Crystal structures of 1:1 complexes between perfluoroarenes and arenes of mismatched geometry have also been reported.^[9–14] Because the geometric arrangement in the solid state is to some extent predictable, fluorinated compounds have been prepared with the aim of engineering their geometric orientation in the crystal.^[15–17]

We were particularly interested in using perfluoroarene – arene interactions to aggregate polymers in solution. While a number of noncovalent interactions are well investigated in polymeric systems,^[18–20] no case has been reported where perfluoroarene – arene interactions were employed. Our idea was to modify either end of the polymer chain with aromatic groups in the hope that they would form alternating stacks in the presence of a perfluorinated additive in solution. Association by the end groups would increase the molecular weight, this could easily be shown by an increase of viscosity. Naphthalene as the aromatic group at the polymer chain end in combination with the perfluorinated additive octafluoronaphthalene (OFN) seemed a good candidate. The stacking behavior of naphthalene with OFN in the solid state is well known, the 1:1 complex between naphthalene and OFN shows an increased melting temperature of around $45\text{--}50^\circ\text{C}$ with respect to either stacking partner and many naphthalene derivatives are commercially available or synthetically accessible in few reaction steps.

Initial experiments with nonpolar polymers, such as poly(norbornene), poly(cyclooctadiene), and others prepared by ring-opening metathesis polymerization (ROMP), with naph-

[*] Prof. Dr. R. H. Grubbs, Dr. A. F. M. Kilbinger
California Institute of Technology
Division of Chemistry and Chemical Engineering
Mail code 164-30, Pasadena, CA 91125 (USA)
Fax: (+1) 626-5649297
E-mail: rhg@caltech.edu

[**] We thank the Office of Naval Research for funding this work. AFMK thanks the Humboldt-Foundation for a Feodor-Lynen Fellowship. We thank Rob Lammertink for help with the rheology measurements.

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

thalene end groups were unsuccessful. As these materials were only soluble in nonpolar solvents, solvation of the naphthalene end groups as well as the perfluorinated additive probably prevented stacking in solution. To gain access to solutions of more polar solvents and to make use of solvophobic effects, we chose to modify poly(ethylene glycol)s (PEGs) with aromatic groups (Figure 1). PEGs are

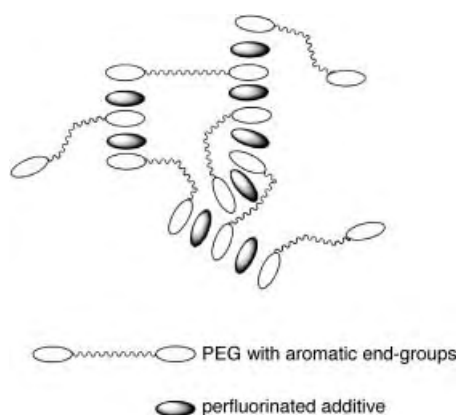
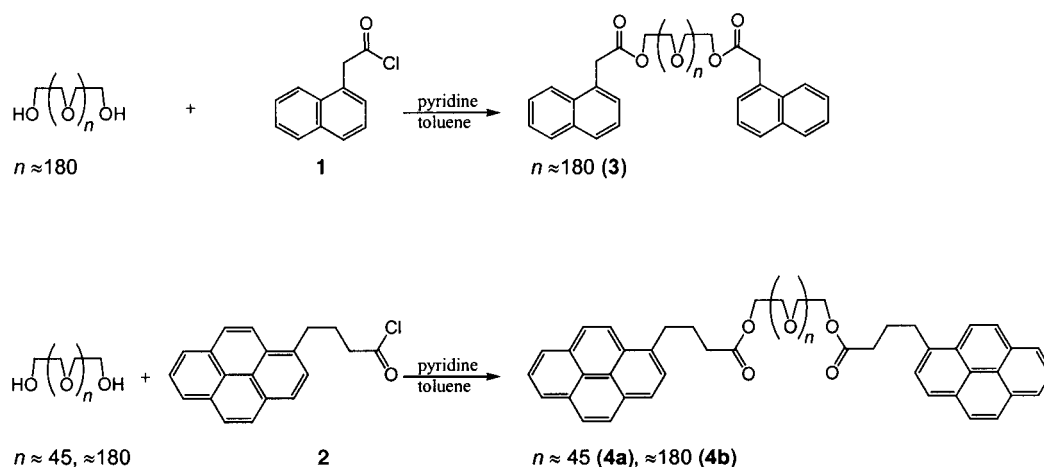


Figure 1. Graphical representation showing PEG chains with aromatic end groups and a possible way of aggregation by face-to-face stacks in the presence of a perfluorinated additive. It is not clear however, what the exact structures of the aggregates are.

soluble in a wide variety of solvents, including organic solvents of low polarity, such as dichloromethane or toluene, as well as in methanol or water. 1-Naphthyl acetoxy chloride (**1**) was used to end cap commercially available PEG ($M_n = 8000$) as the diester **3** (Scheme 1, top). While **3** shows good solubility in common organic solvents, such as chloroform, dichloromethane, or methanol, addition of OFN resulted in clear solutions without any increase of viscosity. OFN added to aqueous solutions of **3** did not dissolve upon heating or sonication and the resulting heterogeneous mixture did not exhibit any increased viscosity. Dissolving OFN in the melt of **3** followed by addition of water also resulted in a heterogeneous mixture of both solid OFN and dissolved polymer and no viscosity increase.

Of all the other stacking partners for OFN (m.p. = 87 °C) reported, pyrene (m.p. = 149 °C) is the one with the highest increase in melting temperature for the 1:1 complex (m.p. = 255,^[21] 248–250^[14]) compared to the individual stacking partners. We therefore changed our strategy and used 1-pyrene butyryl chloride (**2**) to end cap PEGs ($M_n = 2000$ and $M_n = 8000$) as the diesters **4a** and **4b** (Scheme 1, bottom). Both materials show good solubility in organic solvents and water. Dissolving OFN (2 equiv) in the melt of **4a** (1 equiv), letting it solidify, and adding water to the binary mixture, resulted in a slight swelling of the material but the amount of water retained in the material appeared to be low. On the other hand, a material prepared from **4b** and OFN (1:2), formed viscous liquids exhibiting higher viscosities than **4b** in water in the absence of OFN. It is possible that because of the higher concentration of end groups in **4a** than **4b** a cross-linked network was formed which only allowed small amounts of water to be incorporated into the network structure. By increasing the molecular weight of the PEG in **4b** the concentration of end-groups was effectively reduced which lead to a material that dramatically changed viscosity depending on the presence of the perfluorinated additive, OFN.

To show unambiguously that the viscosity increase was induced by the presence of the perfluorinated additive, we measured relative viscosities of aqueous **4b** solutions in the presence (**4b**:OFN = 1:2) and in the absence of OFN at various concentrations (Figure 2). The viscosity of **4b**/OFN is greatly enhanced compared to that of pure **4b** solutions. To ensure that the phenomenon was not the result of a non-specific interaction between the pyrene end groups and OFN, non-fluorinated naphthalene was added to aqueous **4b** solutions. In this case, a heterogeneous mixture was formed and no viscosity increase could be observed. To exclude covalent cross-linking, a sample of **4b** was examined by gel permeation chromatography (GPC) before and after aggregation with OFN. Both samples eluted at the same retention time and covalent cross-linking could be excluded. Aqueous solutions of **4b** and OFN (**4b**:OFN = 1:2) show a decrease in viscosity with increasing temperature (Figure 3) up to about 40 °C where a plateau of constant viscosity is reached. The process is reversible upon cooling. To demonstrate the magnitude of viscosity reached at high concentrations of **4b**



Scheme 1. Synthesis of end-capped PEGs.

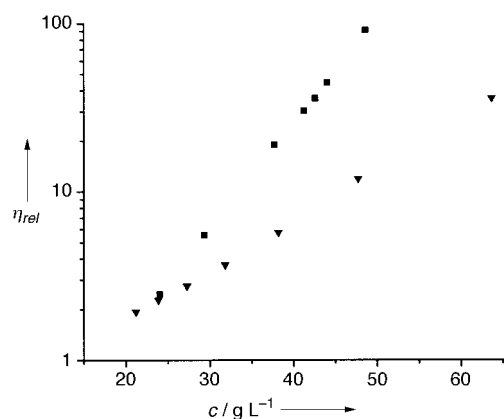


Figure 2. Relative viscosity of **4b** in water (21 °C) at various concentrations. ■: in the presence of two equivalents of OFN, ▼: in the absence of OFN.

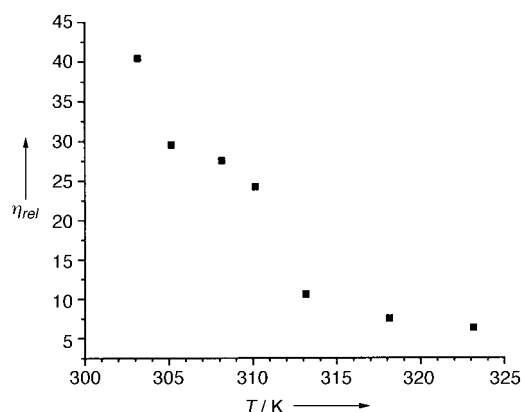


Figure 3. Temperature dependence of the relative viscosity of **4b** ($c = 46.2 \text{ g L}^{-1}$) and 2 mol equivalents of OFN in water.

and OFN (**4b**:OFN = 1:2), zero shear rate viscosities were measured on a rheometer (Figure 4). Very high viscosities were measured in this experiment, clearly showing that a polymer of high molecular weight was formed. The proposed mechanism of aggregation through alternating stacks of aromatic groups favors branched or networked structures

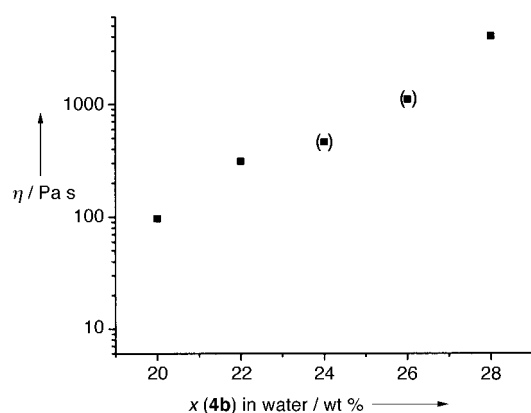


Figure 4. Zero shear rate viscosities of **4b** and 2 mol equivalents of OFN in water (25 °C) at various weight percentages. No steady state was reached during the measurement of 24% and 26% **4b** in water; the data points were extrapolated from the measured data (shown in parenthesis).

over linear ones. However, the physical criterion of network formation, the gel point, could not be observed in our measurements.

To support our assumption, that **4b** associates through alternating stacks of pyrene end groups and OFN in solution, OFN was titrated into a solution of **4b** in water and the fluorescence intensity of the band for monomeric pyrene emission ($\lambda = 377 \text{ nm}$) and the excimer band emission ($\lambda = 480 \text{ nm}$) was plotted against the ratio of OFN to polymer (Figure 5). The intensity of excimer emission decreases with

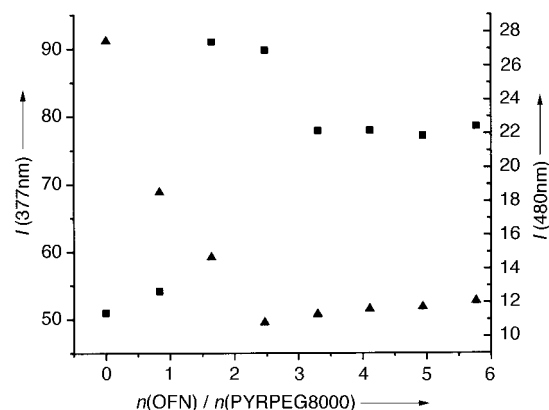


Figure 5. Titration of OFN into a solution of **4b** in water (4 g L^{-1}). The fluorescence intensity at $\lambda = 377 \text{ nm}$ (■; monomer emission) and $\lambda = 480 \text{ nm}$ (▲; excimer emission) are plotted against equivalents of OFN added to the solution.

increasing OFN concentration to reach a plateau at a ratio of approximately two equivalents of OFN per polymer chain while the monomer emission increases and reaches a maximum at the same OFN to polymer ratio. Maitra and D'Souza investigated the binding of OFN to molecular tweezers constructed from pyrene-substituted bile acids.^[22, 23] In their study, an OFN molecule binds between two pyrene moieties of the molecular tweezers which causes the fluorescence emission of monomeric pyrene to increase. However, no decrease of the intramolecular pyrene excimer emission was reported.

If the pyrene end groups of polymer **4b** stacked in an alternating fashion with OFN in solution, the spatial separation of the pyrene units from one another would hinder excimer formation of a photoexcited pyrene unit and hence give rise to an increase of monomeric pyrene emission together with a decrease of excimer emission. At a ratio of two OFN molecules per polymer chain or, in other words one OFN molecule per pyrene end group the system is saturated causing the excimer emission to reach a constant level and the monomer emission to peak.

We have demonstrated that arene–perfluoroarene interactions can act as supramolecular synthons for aggregation not only in the solid state but also in solution. The effect could only be observed in aqueous solutions presumably because of the hydrophobic effect. Nonetheless, it was shown that a specific interaction between the pyrene end groups of the PEG and OFN was responsible for the aggregation phenomenon. Dramatic viscosity changes in the presence of the

perfluorinated additive OFN, as well as evidence from fluorescence measurements, show that the supramolecular synthon pyrene–OFN can be used for the association of PEGs in aqueous solution.

Experimental Section

Detailed information on synthesis and characterization is published as Supporting Information.

3–4b: Poly(ethylene glycol) (4 mmol) was melted in a flask and stirred under high vacuum. Toluene (100 mL) and **1** or **2** (12 mmol) were added to the polymer and the mixture heated until a clear solution was obtained. Pyridine (1 mL) was added slowly dropwise to the solution followed by stirring at 80 °C for 12 h. The reaction mixture was cooled to RT, the precipitated pyridinium hydrochloride removed by filtration through Celite (Aldrich) and the toluene solution added dropwise to diethyl ether (1 L). The polymer precipitate was collected by filtration, dried under high vacuum, redissolved in a small amount of dichloromethane and reprecipitated into diethyl ether. After recovering the product by filtration the polymer was dried under high vacuum for 24 h.

General procedure for the preparation of gels: **4b** (1 equiv) was melted at approximately 60 °C and OFN (2 equiv) dissolved in the melt. The melt was cooled to RT where it solidified. A mixture of deionized water and the desired amount of the solid mixture were sealed in a glass vial and heated in a steam bath under stirring for about 10 min until a homogeneous mixture was obtained. Upon cooling to RT a clear yellow gel or viscous liquid was formed.

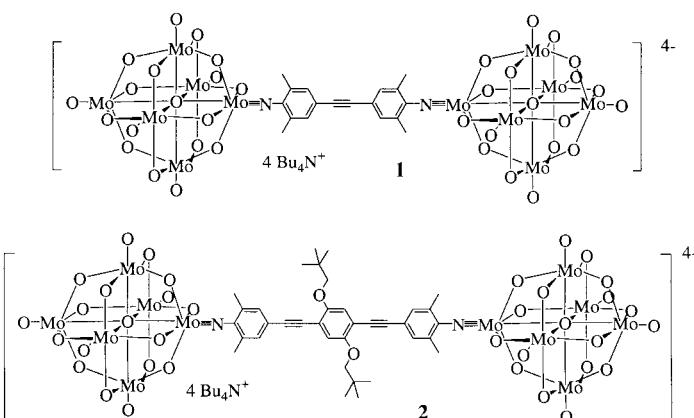
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Hybrid Molecular Dumbbells: Bridging Polyoxometalate Clusters with an Organic π -Conjugated Rod**

Meng Lu, Yongge Wei, Bubin Xu, Calida Fung-Chi Cheung, Zhonghua Peng,* and Douglas R. Powell

We report the facile synthesis of novel hybrid molecular dumbbells in which two polyoxometalate (POM) clusters are covalently bridged by a rigid, π -conjugated organic rod of controllable length. Hybrid materials based on covalently linked POMs and organic species have been extensively studied in recent years.^[1–3] The motivation lies not only in the combinations of “value-adding properties”,^[4] but also in introducing possible synergistic effects. Among the many organic derivatives of POMs, organoimido derivatives have attracted particular interest because the organic π electrons may extend their conjugation to the inorganic framework and thus dramatically modify the redox properties of the cluster.^[4, 5] Moreover, organoimido derivatives of POMs with a remote functionality may be utilized to construct covalently linked POM networks. Here we show that functionalized POM clusters can indeed be utilized to conveniently and efficiently construct POM networks.^[3a] Specifically, we report the synthesis of two novel hybrid dumbbells **1** and **2**, in which two POM cages are linked through an extended π -conjugated organic bridge.^[5c, 6]

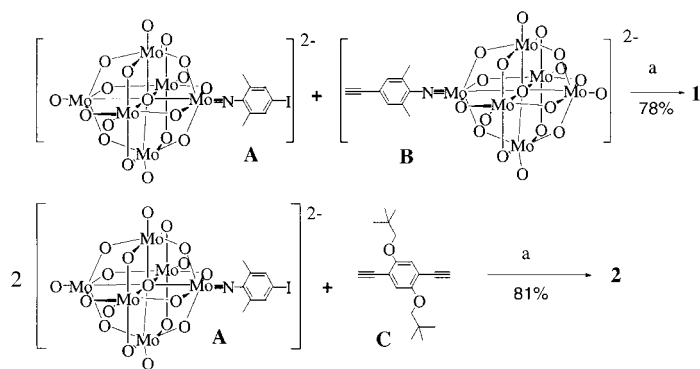


The hybrid dumbbells were synthesized by the Pd-catalyzed Sonogashira coupling reaction.^[7,8] As shown in Scheme 1, direct coupling of the iodo-functionalized hexamolybdate

[*] Prof. Z. Peng, M. Lu, Dr. Y. Wei, B. Xu, C. F.-C. Cheung
Department of Chemistry
University of Missouri – Kansas City
Kansas City, MO 64110 (USA)
Fax: (+1) 816-235-5502
E-mail: pengz@umkc.edu

Dr. D. R. Powell
Department of Chemistry
University of Kansas
Lawrence, KS 66045 (USA)

[**] This work is supported by Research Corporation, National Science Foundation (DMR 0134032) and the Office of Naval Research. Acknowledgement is also made to the Donors of Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.



Scheme 1. Syntheses of hybrid molecular dumbbells. The counteranion is tetrabutylammonium. a) $[\text{PdCl}_2(\text{PPh}_3)_2]$, CuI, K_2CO_3 , Et_3N , CH_3CN , RT.

anion **A** and the ethynyl-substituted analogue **B**, both synthesized by using an approach developed in our laboratory,^[9] gave hybrid **1** in greater than 78% yield of isolated, pure, crystalline product. Hybrid **2**, which has a longer bridge, was prepared by coupling of 2,5-bis(2,2-dimethylpropoxy)-1,4-diethynylbenzene and 2 equiv of **A**. Both reactions proceeded smoothly at room temperature and were completed in less than one hour. Analytically pure products can be obtained by simple recrystallization.

Hybrid **2** shows excellent solubility in common organic solvents such as acetone, acetonitrile, dichloromethane, and chloroform, but hybrid **1** is only slightly soluble in these solvents. Their ^1H NMR spectra (in CD_3CN) are shown in Figure 1. The spectrum of **1** is nearly identical to that of **B** except for the absence of the signal for the ethynyl proton at $\delta = 3.65$. The signals for the aromatic and methyl protons appear as singlets at $\delta = 7.22$ and 2.59, respectively. The remaining peaks correspond to the protons of the tetrabutylammonium cation. The spectrum of **2** has, in addition to the peaks found in **1**, three additional signals at $\delta = 7.06$, 3.71, and 1.09. These three singlets correspond to the aromatic protons on the central phenyl ring, the methylene protons linked to the oxygen atom, and the benzyl methyl protons, respectively. Both spectra show clearly resolved signals, all of which can be unambiguously assigned (see Figure 1 for complete assignment).

The electronic properties of the hybrid dumbbells were studied by UV/Vis absorption and fluorescence measurements. As shown in Figure 2, the lowest energy electronic transition exhibits a significant bathochromic shift on going from **A** (362 nm) and **B** (368 nm) to **1** (426 nm) and **2** (438 nm), and this indicates that the Mo–N π electrons are delocalized over the organic conjugated π system. In other words, there is strong electronic interaction between the metal–oxygen cluster and the organic conjugated segment. Static fluorescence studies show that hybrids **1** and **2** show no fluorescence under excitation from 200 to 500 nm. Since oligo(phenylene ethynylene)s are strongly fluorescent molecules,^[10] the hexamolybdate cluster clearly acts as a fluorescence quencher, presumably by accepting the excited electrons.

The molecular structure of **1** was determined by single-crystal X-ray diffraction.^[11] Compound **1** crystallizes in the

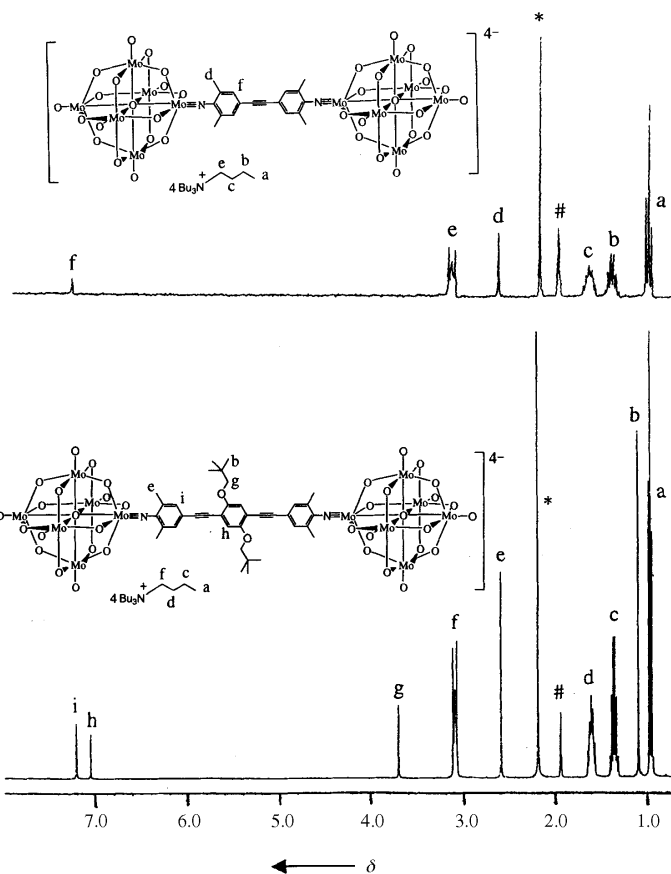


Figure 1. ^1H NMR spectra of **1** and **2**. The peaks marked with * and # correspond to the protons of acetone and acetonitrile, respectively.

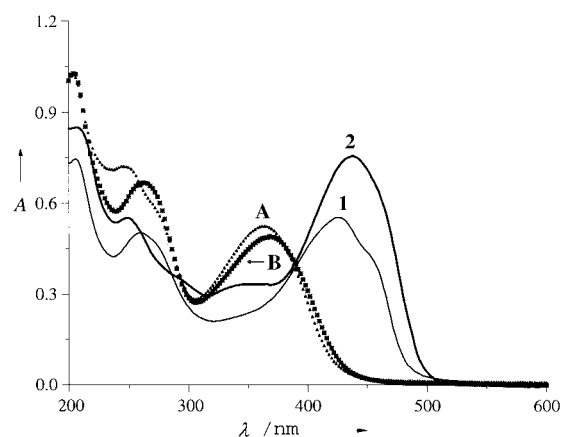


Figure 2. UV/Vis absorption spectra of **1**, **2**, **A**, and **B** in acetonitrile.

monoclinic space group $P2_1/c$. Each cluster anion sits on a crystallographic center of symmetry, so that only one half of an anion is included in the asymmetric unit. As expected, the anion of **1** (Figure 3) is indeed made up of two terminally substituted imidohexamolybdate cages bridged by a *para*-disubstituted, conjugated, rodlike aromatic system. This cluster anion has crystallographically imposed ideal C_i symmetry with the inversion center located at the middle of the $\text{C}\equiv\text{C}$ bond. As a result of the slight bending of the Mo–N–C bonds (172.8° bond angle), the hybrid dumbbell adopts a flattened S-shape. The slight bending of the $\text{C}-\text{C}\equiv\text{C}$ bonds results in a minor vertical displacement of the two parallel

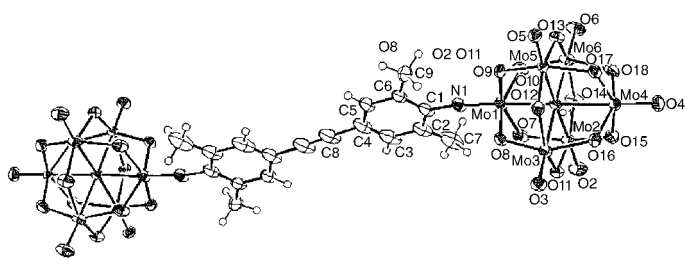


Figure 3. ORTEP plot of the anion of **1** (50% probability thermal ellipsoids for non-hydrogen atoms) showing the atom-labeling scheme for the asymmetric unit. Selected bond lengths [Å] and angles [°]: C1–N1 1.381(4), Mo1–N1 1.744(3), Mo1–O1 2.211(2), Mo2–O2 1.692(3), Mo2–O1 2.330(2), Mo3–O3 1.689(2), Mo3–O1 2.327(2), Mo4–O4 1.687(3), Mo4–O1 2.359(2), Mo5–O5 1.694(2), Mo5–O1 2.331(2), Mo6–O6 1.686(3), Mo6–O14 2.029(3), Mo6–O1 2.350(2); C1–N1–Mo1 172.8(3), N1–Mo1–O7 100.51(14), N1–Mo1–O10 102.87(13), N1–Mo1–O9 103.11(13), N1–Mo1–O8 101.02(12), N1–Mo1–O1 178.28(12).

phenyl rings. The hexamolybdate cages in **1** show features typical of other arylimido derivatives:^[5] the Mo–N bond has substantial triple bond character, as evidenced by its short bond length and near linear Mo–N–C bond angle; the central oxygen atom inside the cluster cage is drawn closer to the imido-bearing Mo atom; the equatorial Mo₄O₄ belt perpendicular to the long axis of the molecule shows regular short–long bond length alternation. Careful comparison of the bond lengths of **1** with those of **A** and **B** reveals some notable differences. In **1**, the bond between the central oxygen atom and the imido-bearing Mo atom and the N–C bond are shorter, while the Mo–N bond is longer than the corresponding bonds in **A** and **B**. These results indicate stronger π -electron delocalization among the molecular axes, which makes the bond-length alternation less pronounced.

In conclusion, we have demonstrated that functionalized organoimido derivatives of polyoxometalates can be utilized to construct covalently linked POM hybrids. The modular building block approach introduces the advantages of versatility, flexibility, and controllability of organic reactions into the synthesis of covalently linked POM/organic hybrids with predetermined structures. The strong electronic interactions between the POM clusters and the conjugated organic bridge in these hybrid molecular dumbbells makes them an interesting new class of electrically active materials. In addition to molecular dumbbells, many other POM/organic hybrids linked in a variety of geometries can in principle be prepared by similar approaches.

Experimental Section

1: A mixture of **A** (0.75 g, 0.5 mmol), **B** (0.80 g, 0.5 mmol), [PdCl₂(PPh₃)₂] (10 mg, 0.01 mmol), copper(I) iodide (6 mg, 0.02 mmol), K₂CO₃ (anhydrous, 1.0 g, 7 mmol), triethylamine in acetonitrile (0.5 mL of a 1 M solution, 0.5 mmol), and acetonitrile (20 mL) was stirred at room temperature for about 30 min under nitrogen. The resulting dark red solution was added to CH₂Cl₂ (100 mL), washed twice with brine, and then concentrated to about 30 mL. After the addition of ethyl acetate (100 mL), the solution was left standing without disturbance for about 8 h. The orange precipitate was collected by filtration and washed successively with dichloromethane and acetone. It was further purified by recrystallizing twice from acetone (yield: 1.16 g, 78%). The single crystals used for X-ray diffraction were obtained by diffusion of ethyl acetate into a solution of **1** in DMF. Elemental analysis (%) calcd for C₈₂H₁₆₀N₆O₃₆Mo₁₂: C 33.30, H 5.45, N 2.84; found: C 33.06, H

5.53, N 2.80. ¹H NMR (250 MHz, CD₃CN, 25 °C, TMS): δ = 7.22 (s, ArH, 4H), 3.09 (t, J = 8.50 Hz, NCH₂, 32H), 2.59 (s, (Ar)CH₃, 12H), 1.60 (q, J = 7.94 Hz, CH₂, 32H), 1.35 (H, J = 7.25 Hz, CH₂, 32H), 0.96 (t, J = 7.25 Hz, CH₃, 48H); UV/Vis (MeCN): λ /nm (ϵ /M^{−1}cm^{−1}) = 206 (1.40 × 10⁵), 260 (9.43 × 10⁴), 426 (1.04 × 10⁵).

2: A mixture of **C** (0.5 mmol), **A** (1.75 g, 1.1 mmol), [PdCl₂(PPh₃)₂] (40 mg, 0.057 mmol), copper(I) iodide (20 mg, 0.1 mmol), triethylamine (1 mL), and acetonitrile (40 mL) was stirred under nitrogen for 1 h at room temperature. The dark red solution was added to CH₂Cl₂ (300 mL) and washed twice with water. The organic layer was collected, and its solvent removed by vacuum evaporation. Acetone (20 mL) was added to the residue. The resulting suspension was filtered through a syringe filter (0.2 μ m), and the filtrate was concentrated to ca. 10 mL. The concentrated solution was added slowly to diethyl ether (200 mL). After standing for 10 min, the top layer of solvents was decanted. The oily residue was dried under vacuum overnight to give a dark red powder, which was purified by recrystallization from acetone/diethyl ether to yield analytically pure product (81%). Elemental analysis (%) calcd for C₁₀₀H₁₈₂N₆O₃₈Mo₁₂: C 37.21, H 5.68, N 2.60; found: C 37.60, H 5.24, N 2.33. ¹H NMR (400 MHz, CD₃CN, 25 °C): δ = 0.96 (t, J = 7.25 Hz, 48H, CH₃), 1.09 (s, 18H, CH₃), 1.35 (m, 32H, CH₂), 1.59 (m, 32H, CH₂), 2.60 (s, 12H, ArCH₃), 3.10 (m, 32H, NCH₂), 3.71 (s, 4H, OCH₂), 7.05 (s, 2H, ArH), 7.21 (s, 4H, ArH); ¹³C NMR (400 MHz, CD₃CN, 25 °C): δ = 14.2, 18.8, 20.7, 24.7, 27.2, 33.2, 59.6, 80.4, 89.7, 95.9, 114.9, 123.4, 131.2, 139.7, 154.6, 155.3; UV/Vis (MeCN): λ _{max}/nm (ϵ /M^{−1}cm^{−1}) = 206 (1.36 × 10⁵), 250 (8.82 × 10⁴), 438 (1.24 × 10⁵).

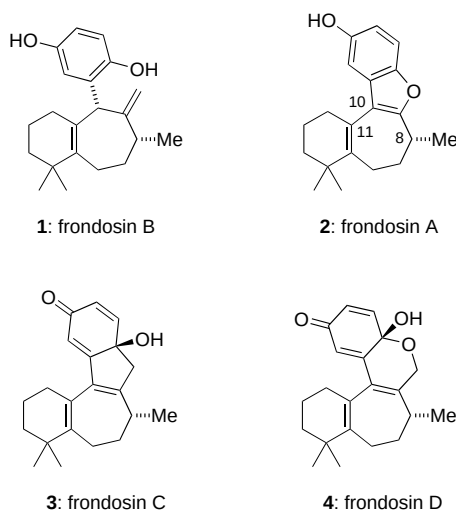
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Concise Total Synthesis of (–)-Frondosin B Using a Novel Palladium-Catalyzed Cyclization**

Chambers C. Hughes and Dirk Trauner*

The frondosins (Scheme 1), a family of marine terpenoids isolated from the sponge *Dysidea frondosa*, have been found to inhibit the binding of interleukin-8 (IL-8) to its receptor in the low micromolar range.^[1a] IL-8, which is produced by macrophages and endothelial cells, recruits T-lymphocytes



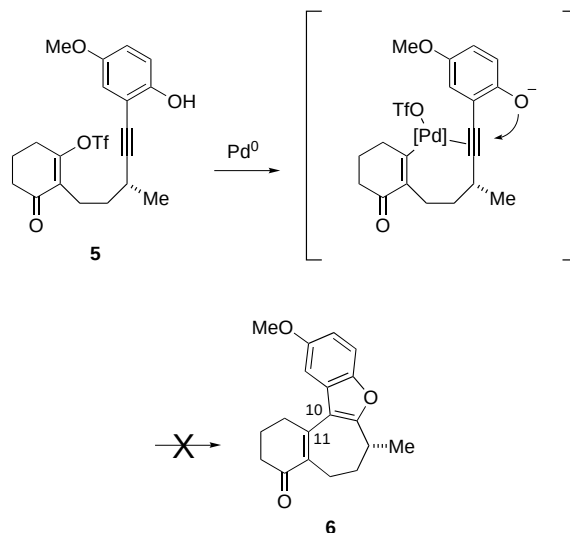
Scheme 1. The frondosins. The absolute stereochemistry shown is arbitrary.

and neutrophils to an inflammatory site and is implicated in a wide range of acute and chronic inflammatory disorders. IL-8 receptor antagonists like the frondosins, therefore, interfere with the inflammatory cascade and might ultimately be used to prevent autoimmune disorders such as rheumatoid arthritis and psoriasis. Equally important, members of the frondosin family have also been shown to exhibit HIV-inhibitory properties.^[1b]

Recently, (+)-frondosin B (**1**) has attracted much attention. The first total synthesis of this interesting norsesquiterpenoid by the Danishefsky group confirmed the structure and led to the assignment of an absolute configuration.^[2] Although **1** features only one stereocenter, it represents a considerable synthetic challenge because of its unusual tetracyclic skeleton, which incorporates a 2,3-disubstituted benzofuran moiety and a readily isomerized tetrasubstituted double bond.

A key connection, also noticed by others,^[2] is the formation of the bond between C10 and C11 to establish the central seven-membered ring of the target. Our original plan foresaw the implementation of the Arcadi–Cacchi reaction^[3] for the

construction of the tetracyclic core from an alkynyl phenol precursor of type **5** (Scheme 2). No intramolecular version of this palladium-catalyzed reaction has been reported to date. Despite efforts to convert **5** into **6** with a range of palladium reagents, however, we were unable to effect the desired cyclization. Instead, extensive decomposition of the starting material took place.



Scheme 2. Initial strategy for the key cyclization in the synthesis of frondosin B (**1**). Tf = trifluoromethanesulfonyl.

Attempting to gain more insight into the mechanism of the Arcadi–Cacchi reaction, we found that efficient, palladium-catalyzed bond formation could indeed be achieved provided the benzofuran moiety was already in place. This observation greatly simplified and streamlined our overall synthetic plan, as the formation of the free phenol **5**, unlike the corresponding benzofuran **15** (see below), could be realized only through difficult protective group manipulations.

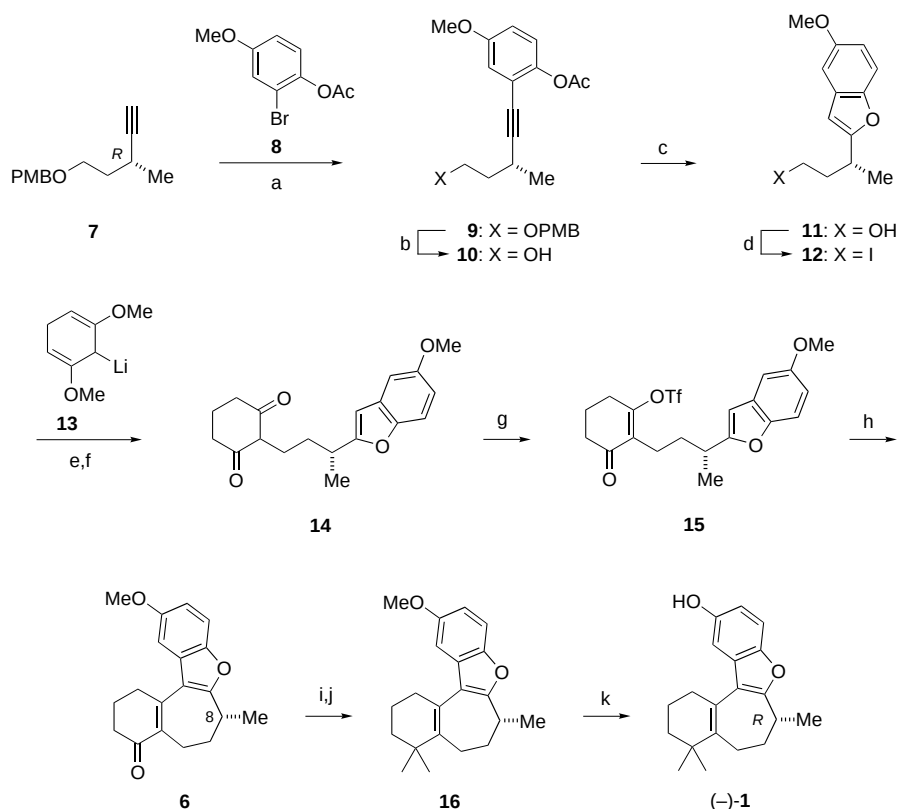
Our synthesis starts with the known *R*-configured alkyne **7**^[4] (obtained in 91 % *ee* by means of a Sharpless epoxidation) and the known aryl bromide **8**^[5] (Scheme 3). Sonogashira coupling^[6] of these two components followed by acidic deprotection^[7] gave the primary alcohol **10**. Subsequent saponification of the phenolic acetate with concomitant cyclization afforded benzofuran **11** in high yield. This material was then converted to the corresponding iodide **12**. Alkylation of dimethoxylithiocyclohexadiene **13** by using the Piers protocol^[8] followed by hydrolysis afforded cyclohexa-1,3-dione **14**.^[9] This surprisingly unstable diketone decomposed on standing and was therefore immediately converted into enol triflate **15** by which the stage for the key cyclization was set.

The key bond formation between C10 and C11 was achieved in good yield by heating **15** with a catalytic amount of [Pd(PPh₃)₄] in dimethyl acetamide (DMA) in the presence of Hünig's base.^[10] Importantly, no detectable racemization of the C8 stereocenter occurred under these conditions (see *Experimental Section*).^[11]

The conversion of the carbonyl group into a *gem*-dimethyl moiety was achieved by using a protocol developed by Reetz

[*] Prof. D. Trauner, C. C. Hughes
Center for New Directions in Organic Synthesis
Department of Chemistry
University of California, Berkeley
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-643-9480
E-mail: trauner@cchem.berkeley.edu

[**] This work was supported by a generous gift from Merck & Co.



Scheme 3. Total synthesis of (–)-frondosin B (–)-**1**. a) $[\text{Pd}(\text{PPh}_3)_4]$, CuI , Et_3N , MeCN , reflux, 94 %; b) TFA , CH_2Cl_2 , RT, 83 %; c) K_2CO_3 , MeOH , reflux, 92 %; d) MsCl , Et_3N , THF , 0°C , then NaI , Me_2CO , reflux, 93 %; e) **13**, HMPA , THF , $-78^\circ\text{C} \rightarrow \text{RT}$, 85 %; f) ion-exchange resin, Me_2CO , H_2O , reflux; g) NaHMDS , PhNTf_2 , THF , Et_2O , RT, 75 % (2 steps); h) $[\text{Pd}(\text{PPh}_3)_4]$, DMA , $i\text{Pr}_2\text{NEt}$, 90°C , 70 %; i) MeMgBr , THF , $-78^\circ\text{C} \rightarrow \text{RT}$; j) Me_2Zn , TiCl_4 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 82 % from **6**; k) NaSEt , DMF , reflux, 90 %. $\text{PMB} = \text{para-methoxybenzyl}$, $\text{TFA} = \text{trifluoroacetic acid}$, $\text{Ms} = \text{methanesulfonyl}$, $\text{HMPA} = \text{hexamethylphosphoramide}$, $\text{NaHMDS} = \text{sodium bis(trimethylsilyl)amide}$, $\text{DMA} = N,N\text{-dimethylacetamide}$.

et al.^[12] As a result of the low electrophilicity of the vinyl-ogous aryl ketone, this procedure had to be carried out in two separate steps. Reaction of ketone **6** with MeMgBr gave the corresponding crude, highly acid-sensitive tertiary alcohol, which was subsequently subjected to the action of $[\text{Me}_2\text{TiCl}_2]$ (formed in situ from Me_2Zn and TiCl_4). This afforded *O*-methyl frondosin B (**16**) in good overall yield. Finally, *O*-demethylation following a previously reported procedure gave frondosin B (**1**) in high optical purity.^[2]

To our surprise, however, the optical rotation of the (*R*)-configured material thus obtained was opposite to that of the natural product ($[\alpha]_{\text{D}}^{25} = -16.8$ compared to $[\alpha]_{\text{D}} = +18.6$ ^[1a]). Though the natural product had been assigned the *R* configuration in the synthesis by Danishefsky et al., according to our work, (+)-frondosin B is *S*-configured. Having ruled out trivial mistakes, we were left with the puzzling possibility that either Danishefsky's or our material had undergone an unnoticed inversion of configuration at some stage (see below).

For the key cyclization **15** $\rightarrow$ **6**, several mechanistic scenarios can be imagined. Control experiments with various Lewis acids (e.g. ZnCl_2 , MgBr_2 , $\text{BF}_3 \cdot \text{OEt}_2$) gave no product, which suggests that the reaction does not proceed by means of conjugate addition/elimination. Nucleophilic catalysis by

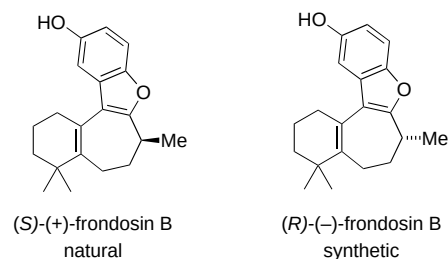
triphenylphosphane or amines was also excluded. Thus, it appears that oxidative addition of palladium to the carbon–oxygen bond of the triflate is essential and that this is a genuine palladium-catalyzed reaction.

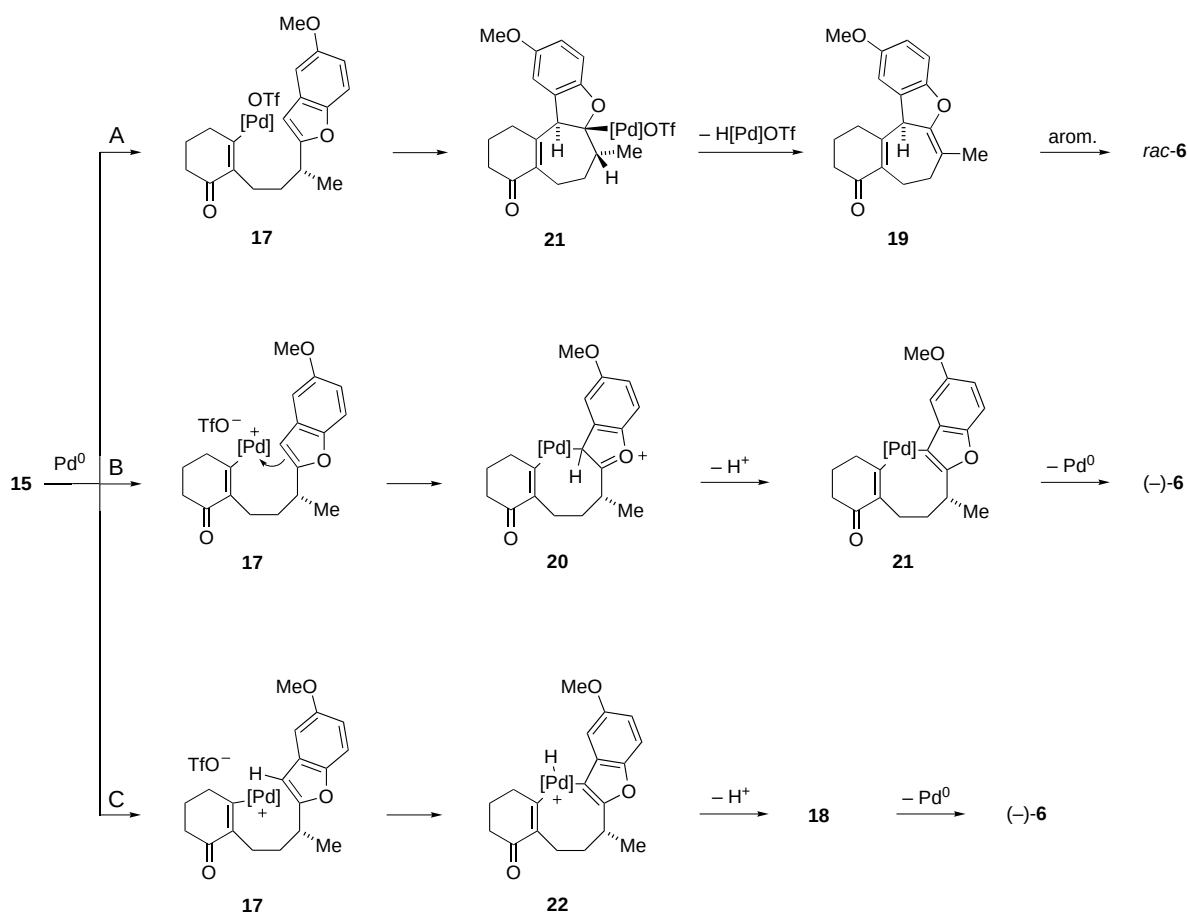
Although isolated examples of Heck reactions involving furans have been reported,^[13] none have been used in the total synthesis of a natural product.^[14] Moreover, no benzofurans have been employed as substrates. The fact that the stereocenter at C8 does not racemize under the reaction conditions raises the question whether a standard Heck mechanism involving oxidative addition (**15** $\rightarrow$ **17**), migratory insertion (**17** $\rightarrow$ **18**), and β -hydride elimination (**18** $\rightarrow$ **19**) operates (Scheme 4, pathway A). Provided that the product of migratory insertion, **18**, undergoes *syn*-elimination of a hydridopalladium species, racemization would be expected upon rearomatization of the resulting enol ether **19**.

Since racemization does not occur, however, an alternative mechanism may be operating (Scheme 4, pathways B and C). In the first, oxidative addition is followed, instead, by nucleophilic attack of the electron-rich benzofuran onto the palladium(II) intermediate **17**, which is possibly cationic in nature. Deprotonation of the cationic intermediate **20** then affords

21, which reductively eliminates Pd^0 to yield the product (–)-**6** with the stereocenter at C8 left intact. In the second, the highly electrophilic, cationic palladium species **17** undergoes intramolecular C–H insertion^[15] to afford the palladium(IV) intermediate **22**, which upon loss of a proton and reductive elimination again gives (–)-**6**.

If mechanism A applies, the rearomatization of **19** may possibly occur in a completely stereoselective fashion and lead to inversion of the stereocenter at C8.^[16] It appears, however, that the absolute configuration was unintentionally switched as a result of neighboring group participation in an early stage of the previous synthesis.^[17, 2b] We therefore suggest that naturally occurring (+)-frondosin B (**1**) corresponds to the *S* isomer.^[18]





Scheme 4. Mechanism of the key cyclization.

In summary, we have achieved an expedient, asymmetric total synthesis of (-)-frondosin B (**1**) from simple starting materials (22% overall yield from the known alkyne **7**). The salient features of the synthesis include two palladium-catalyzed reactions: an efficient Sonogashira coupling with an aryl bromide and a novel cyclization onto a benzofuran. Furthermore, the usefulness of the Reetz protocol for installing a *gem*-dimethyl group in a natural product has been demonstrated. Studies toward the synthesis of other members of the frondosin family are underway and will be reported in due course.

Experimental Section

To a degassed solution of *i*Pr₂NEt (0.78 mL, 4.5 mmol) in dry DMA (110 mL) was added [Pd(PPh₃)₄] (65 mg, 0.056 mmol), and the mixture was heated under Ar to 90 °C. A solution of triflate **15** (500 mg, 1.12 mmol) in dry DMA (5 mL) was then added with a syringe pump over 3 h. The reaction mixture was stirred at 90 °C for an additional 36 h, cooled, diluted with saturated aqueous bicarbonate solution, and extracted four times with Et₂O (200 mL). The combined Et₂O extracts were washed twice with water (100 mL), once with brine (50 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (15% EtOAc in hexanes) to afford 234 mg (70%) of **6** as a viscous oil: $[\alpha]_D^{25} = -36.1$ ($c = 1.00$, CHCl₃); IR (film): $\tilde{\nu} = 2934, 1656, 1474 \text{ cm}^{-1}$; ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 7.33$ (d, $J = 8.8 \text{ Hz}$, 1H), 7.16 (d, $J = 2.4 \text{ Hz}$, 1H), 6.87 (dd, $J = 8.8 \text{ Hz}$, 2.4 Hz, 1H), 3.85 (s, 3H), 3.28 (m, 1H), 3.06–2.95 (m, 2H), 2.80 (m, 1H), 2.59–2.47 (m, 2H), 2.35 (m, 1H), 2.17–2.04 (m, 3H), 1.55 (m, 1H), 1.38 (d, $J = 6.8 \text{ Hz}$, 3H); ¹³C NMR (75 MHz, CDCl₃, 25 °C): $\delta = 197.6, 164.5, 156.0, 149.3, 149.1, 137.2, 128.3,$

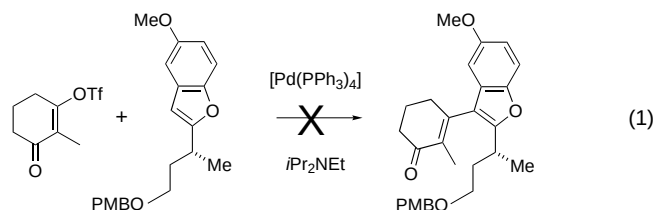
115.8, 111.7, 111.5, 105.9, 56.3, 37.9, 36.1, 35.1, 30.9, 23.7, 21.4, 20.6; HRMS (EI) m/z calcd. for C₁₉H₂₀O₃, 296.1412; found, 296.1414. The enantiomeric excess was determined by HPLC [Chiralpak ADTM column, 2% *i*PrOH in hexanes at 1.0 mL min⁻¹; t_R (major enantiomer) = 25.8 min, t_R (minor enantiomer) = 33.8 min] to be 91% (e.r. = 95.5:4.5).

Received: October 18, 2001

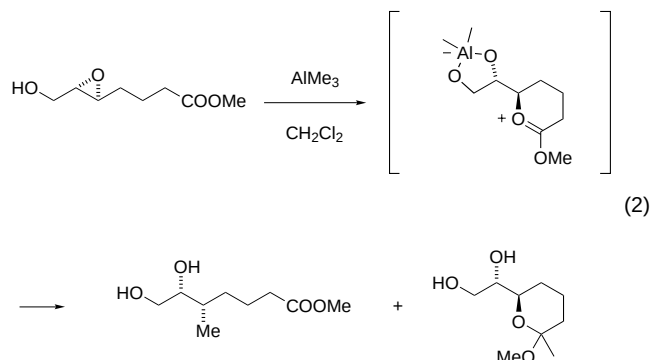
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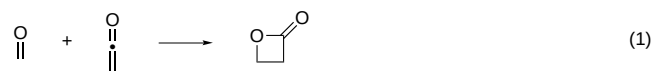
- [18] Attempts to assign the absolute configuration of frondosin B independently by X-ray crystallographic analysis of its bromobenzoate and camphanoyl ester have thus far been unsuccessful.

Mechanism and Origin of Stereoselectivity in Lewis Acid Catalyzed [2 + 2] Cycloadditions of Ketenes with Aldehydes**

Daniel A. Singleton,* Yingcai Wang, Hong Woon Yang, and Daniel Romo*

Stereoselectivity as a general phenomenon arises from differences in free energy associated with diastereomeric transition states or diastereomeric products. Free-energy differences between diastereomeric pathways are a requirement for stereoselectivity, but they are not sufficient in themselves. For example, high kinetic enantioselectivity may be compromised by product racemization. Another common situation is when stereoisomeric products are formed by differing mechanisms, so the inhibition of alternative mechanisms is often pivotal in the development of stereoselective methodology. A more complex possibility is that stereoisomeric pathways may have different rate-limiting steps.^[1] We describe here evidence for such an event in a cycloaddition in which diastereomeric products are formed, and we discuss the impact of divergent rate-limiting steps on selectivity.

β -Lactones are exceptionally versatile intermediates in organic synthesis,^[2] and there has been considerable interest in their direct synthesis from the [2 + 2] cycloaddition of ketenes with carbonyl compounds [Eq. (1)].^[3] A growing number of variants employ achiral^[4] or chiral^[5] Lewis acid catalysts to afford optically enriched β -lactones by substrate or reagent control, respectively.



The synthetic utility and fundamental allure of these formally forbidden cycloadditions make their mechanism of considerable interest. Experimental studies have been limited to substituent, solvent, and stereochemical effects in the uncatalyzed reaction,^[6] but several theoretical studies have

[*] Prof. D. A. Singleton, Prof. D. Romo, Y. Wang
Department of Chemistry
Texas A & M University
P.O. Box 30012, College Station, TX 77842-3012 (USA)
Fax: (+1) 979-845-5719
E-mail: singleton@mail.chem.tamu.edu
romo@mail.chem.tamu.edu

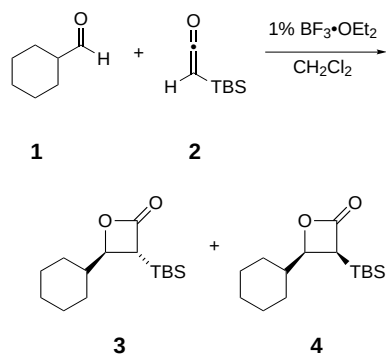
Dr. H. W. Yang
Department of Chemistry
Johns Hopkins University
3400 North Charles Street, Baltimore, MD 21218 (USA)

[**] We thank the NIH (GM-45617, D.A.S.), the NSF (CAREER Award to D.R., CHE-9624532), and the Robert A. Welch Foundation (A-1145, D.A.S.; A-1280, D.R.) for support, and the NSF (CHE-9528196) and the Texas A&M University Supercomputing Facility for computational resources. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. The NSF (CHE-0077917) also provided funds for purchase of NMR instrumentation.

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looked at both the uncatalyzed and Lewis acid catalyzed cycloadditions. For the uncatalyzed process, AM1 calculations predict a stepwise process but Hartree-Fock (HF), CASSCF, and density functional theory (DFT) calculations all favor a concerted mechanism involving a $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ transition state.^[7] Similarly for Lewis acid catalyzed reactions, AM1 calculations on the reaction of formaldehyde · BF₃ with ketene predict a stepwise process involving a zwitterionic intermediate,^[8] while HF calculations employing an Onsager-type solvent model for the cycloaddition of acetaldehyde · BH₃ with chloroketene favor a concerted asynchronous mechanism.^[7c] The conflicting predictions, the use of simplified model systems, and intrinsic limitations of the calculational methods employed combine to impede a secure understanding of mechanism and selectivity in the Lewis acid catalyzed reaction.

Our goal was to define the stepwise versus concerted nature of the cycloaddition in a synthetically relevant example and to gain insight into its stereoselectivity. Toward that end, the clean, high-yielding BF₃·OEt₂-catalyzed cycloaddition of cyclohexanecarboxaldehyde (**1**) with *tert*-butyldimethylsilylketene (**2**) was chosen for study [Eq. (2); TBS = *tert*-butyldimethylsilyl]. This reaction had previously been reported to afford a 62% yield of a 96:4 ratio of the *trans* and *cis* diastereomeric



(2)

products **3** and **4** (−20 °C, “catalytic” BF₃·OEt₂, 1M HCl workup).^[3c] Under our conditions (0 °C, 1 mol % BF₃·OEt₂, buffered workup) the yield of isolated product was as high as 98% and typically >90%. An intriguing observation in this reaction is that the ratio of **3**:**4** varies substantially with temperature, and the selectivity *decreased* with decreasing temperature (Table 1). No isomerization was observed under the reaction conditions, and all of the reactions appeared devoid of side products by NMR analyses.

The ¹³C kinetic isotope effects (KIEs) for this reaction were determined at natural abundance by NMR spectroscopy.^[9] To determine the ¹³C KIE for the carbonyl carbon atom of **1**,

Table 1. Effect of temperature on *cis/trans* diastereoselectivity of the Lewis acid catalyzed [2 + 2] cycloaddition of **1** with **2** [Eq. (2)].

Entry	Reaction temperature [°C]	3 : 4
1	+23	2.7–3.1:1
2	0	1.4–1.7:1
3	−21	1.3:1
4	−42 → +23	1.1:1

reactions using a limiting amount of **2** and 1% (versus **1**) BF₃·OEt₂ at 0 °C were taken to 10–20% aldehyde conversion. Similarly, the ¹³C KIEs for **2** were determined from reactions using excess **2** and a limiting amount of **1** taken to approximately 10–20% conversion of **2**. Isotope effects were then calculated from the difference in ¹³C isotopic composition of the products **3** and **4**, compared to standard samples of products from reactions taken to completion. In the ¹³C NMR analysis of these samples, the tertiary cyclohexyl ring carbon and the dimethylsilyl carbon signals were used as “internal standards” with the assumption of a negligible isotope effect in these positions. The results from three independent reactions are summarized in Figure 1. The KIEs obtained are directly limited in precision by the precision of the NMR integrations, and these are the most complex molecules analyzed in this manner so far. Given this, the reproducibility of the experimental KIEs from independent measurements is very reasonable.

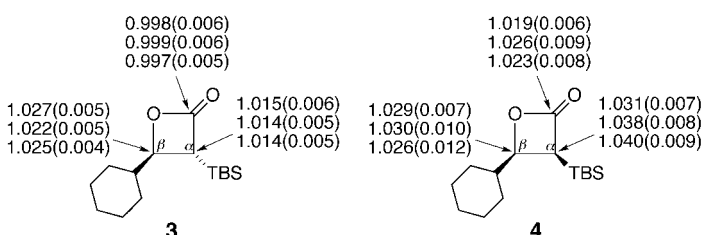
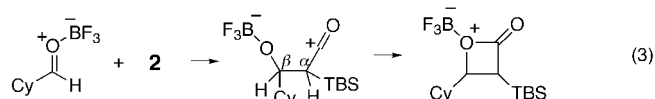


Figure 1. ¹³C KIEs (k_{12C}/k_{13C} , 0 °C) for the BF₃·OEt₂-catalyzed [2 + 2] cycloaddition of **1** with **2**, measured in three independent reactions. Standard deviations from six measurements on each sample are shown in parentheses.

The most striking observation is that the KIEs for the formation of diastereomers **3** versus **4** differ substantially. This is indicative of significantly differing mechanisms or rate-limiting steps in the formation of these products. This is unusual—the Ockham’s-razor assumption is that diastereomeric products are formed by stereoisomeric but otherwise identical pathways. Clearly something more intricate is occurring here.

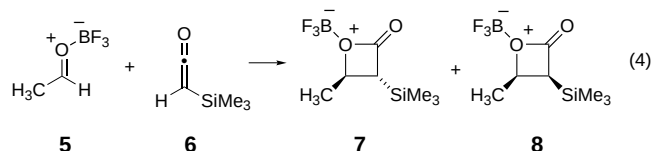
Qualitatively, the observation of significant ¹³C KIEs at the α - and β -carbon atoms of **3**, but no KIE at the carbonyl carbon atom, is suggestive of rate-limiting formation of the C $_{\alpha}$ –C $_{\beta}$ bond of the impending *trans*- β -lactone. This does not preclude a highly asynchronous concerted [2 + 2] cycloaddition, but the most economical hypothesis would be rate-limiting (irreversible) C $_{\alpha}$ –C $_{\beta}$ bond formation [Eq. (3); Cy = cyclohexyl]. In the



formation of the *cis* product **4**, the substantial ¹³C KIEs at all ring carbon atoms would customarily be associated with a concerted cycloaddition. However, it has been recently observed that large secondary ¹³C isotope effects, mimicking primary ¹³C KIEs, can result from the weakened bonds α – β

to charged atoms in reactive intermediates.^[10] Thus a stepwise mechanism can account for significant C_α and C_β KIEs. The KIE of the carbonyl carbon atom in **4** would then be consistent with a rate-limiting second step for a stepwise mechanism.

Theoretical studies buttress these ideas. The model cycloaddition of *anti*-acetaldehyde·BF₃ (**5**) with trimethylsilylketene (**6**) [Eq. (4)] was studied in B3LYP/6-31 + G* calculations, employing an Onsager-type continuum solvent model^[11] for geometry optimizations and a polarizable continuum model (PCM) solvent model for single-point energy calculations.^[12] Both the solvent model and diffuse functions were



required for chemically reasonable results. In the absence of the solvent model, stationary points on the *cis* pathway could not be located, while without diffuse functions the apparent *trans* pathway gave rise to an open-chain acyl fluoride product. A pathway involving *syn*-acetaldehyde·BF₃ had a 5.3 kcal mol⁻¹ higher barrier than those with **5** (see Supporting Information). Efforts to locate transition structures for concerted cycloadditions or for reaction of acetaldehyde with **6**·BF₃ were unsuccessful.

In contrast to previous theoretical studies, the calculations here predict a stepwise cycloaddition mechanism (Figure 2). In this mechanism, initial C–C bond formation via transition structures **9** and **12** leads to zwitterionic intermediates **10** and **13**. Subsequent ring closure forms the *trans*- and *cis*- β -lactone products via the C–O bond-forming transition structures **11** and **14**, respectively.

Most notably, the calculations predict that the first step will be rate limiting for formation of the *trans* product and the second step will be rate limiting for formation of the *cis* product.^[13] The predicted activation barriers of 9.3 and

10 kcal mol⁻¹ are consistent with a reaction that proceeds to completion in a few minutes at 0 °C using 1 mol % catalyst. In accord with the experiment, the activation barriers are predicted to be similar.^[14] It should be noted that the predicted selectivity is very different than if either the first step or the second step were considered by themselves.

The aforementioned decrease in selectivity with decreasing temperature also supports the idea of differing mechanisms or rate-limiting steps in the formation of **3** versus **4**. If **3** and **4** were formed by similar rate-limiting transition states with comparable activation entropies, the selectivity would exhibit the normal tendency to increase with decreasing temperature. The increased preference for **3** at higher temperatures indicates that it is “entropically favored.” This fits with a rate-limiting first step. The confounding effect of solvent entropy imperils predictions of activation entropies for charged reactions, but one might normally expect that the looser first transition state in a stepwise cycloaddition would have greater entropy than the second.

An observation from the closely related TADDOL-TiCl₄ catalyzed cycloadditions of **6** with aldehydes appears relevant. These reactions afford predominantly *cis* α -silylated β -lactones, with moderate enantiomeric excesses determined after separation and desilylation.^[15] The *trans*- β -lactone is formed with much lower enantioselectivity [Eq. (5)]. This is again

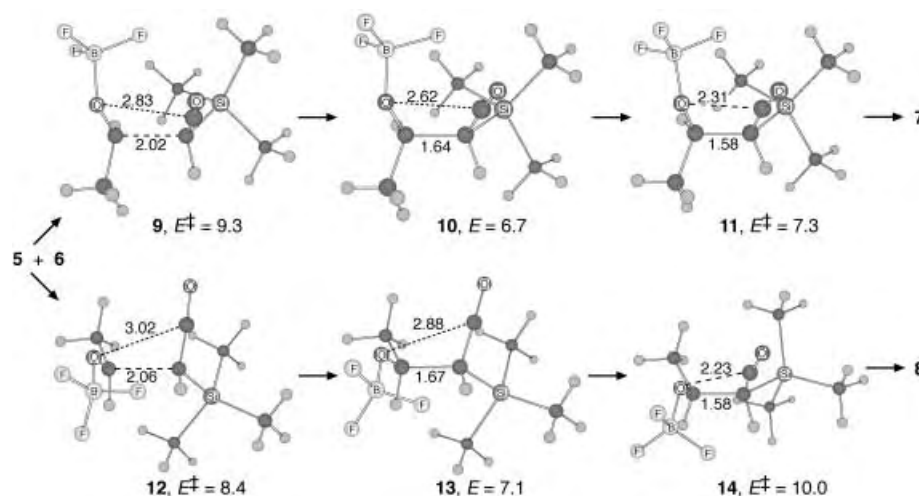
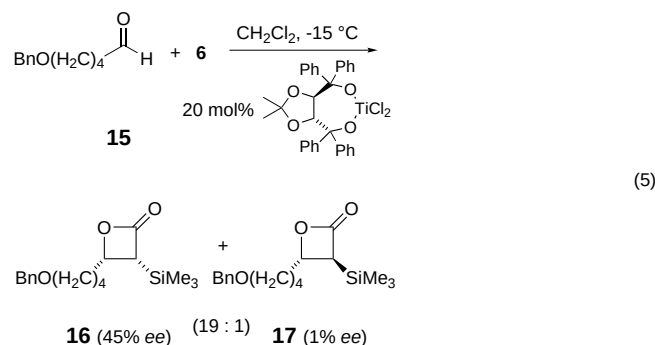


Figure 2. Calculated structures and energies for the cycloaddition of **5** with **6**. Selected distances are given in Å—for complete structures see Supporting Information. Energies are kcal mol⁻¹, relative to **5** + **6**.

consistent with very dissimilar selectivity-determining steps in the formation of the *cis* versus *trans* products.

The results described here suggest a very different rationale for the stereoselectivity of this class of cycloadditions from that proposed by Cosio and co-workers for the reaction of chloroketene with acetaldehyde·BH₃.^[7c] In that work, a preference for the *cis* product with bulky catalysts was attributed to a steric interaction of the catalyst with H versus R¹ in the concerted transition state model **18** (Figure 3a). The present study suggests that formation of *trans* β -lactones proceeds via rate-limiting transition state **9** (Figure 2, cf. **19**, Figure 3b) in which the aldehydic

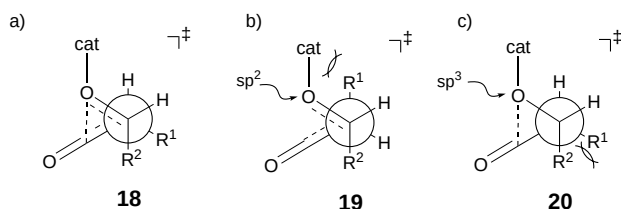


Figure 3. Transition state models for rationalizing stereoselectivity in the [2+2] cycloaddition: a) Cossio's model^[7c)], b) revised model leading to *trans* diastereomer with C–C bond formation as rate-limiting and selectivity-determining step, c) revised model leading to *cis* diastereomer with C–O bond formation as rate-limiting and selectivity-determining step.

oxygen atom is sp^2 hybridized and the Lewis acid is not free to rotate away from steric interactions with the silyl group. Alternatively, transition state structure **14** (Figure 2, cf. **20**, Figure 3c) is rate limiting for the formation of the *cis* product and in this case, the aldehydic oxygen atom is sp^3 hybridized and the Lewis acid can rotate away from steric interactions. Thus, catalyst bulk would have a greater inhibiting effect on formation of the *trans* product (i.e. greater cat./ R^1 interaction) and lead to higher *cis* selectivity as observed. The observation by Yamamoto^[3c)] that bulky groups (R^1) on the ketene favor the *trans* product would be explained by an unfavorable steric interaction with the aldehydic substituent R^2 in **14** (Figure 2, cf. **20**, Figure 3c) which takes on added importance when one considers that C–C bond formation is rate limiting. This observation is not so readily understood from Cossio's model **20** (Figure 3a). Overall, one can conclude that R^1/R^2 interactions are most important during the formation of *cis*- β -lactone diastereomers since these impending eclipsed interactions have the greatest impact on the rate-limiting ring closure (C–O bond formation) following C–C bond rotation. On the other hand, catalyst/ R^1 interactions predominate for the reaction pathway leading to the *trans* diastereomer.

More generally, the observations made in this study highlight that a broad range of factors must be pondered in order to understand and control stereoselectivity in a multistep reaction. Selectivity among competitive pathways may be determined by dissimilar transition states or divergent rate-limiting steps, and a strong energetic preference for one transition state over a stereoisomeric partner is not sufficient to guarantee high stereoselectivity. Rather, stereoselectivity must be controlled throughout a mechanism.

Received: December 5, 2001
Revised: February 15, 2002 [Z18331]

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[14] Owing to a referee's concern over using an unbranched aldehyde as a theoretical model, we have repeated our calculations with isobutyr-aldehyde instead of acetaldehyde and the results are qualitatively identical (see Supporting Information). The energies for the isobutyl analogues of **9–14** (B3LYP/6-31G*/PCM/B3LYP/6-31G*/Onsager + zpe, versus starting materials) are 13.1, 11.0, 11.3, 12.5, 11.6, and 14.6 kcal mol $^{-1}$, respectively.
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Cyclotetrasilene Ion: A Reversible Redox System of Cyclotetrasilanyl Cation, Radical, and Anion**

Tadahiro Matsuno, Masaaki Ichinohe, and Akira Sekiguchi*

Alkali metal derivatives of organosilicon compounds are useful not only in organosilicon chemistry, but also in organic synthesis. The synthesis, reactivity, and structural aspects of silyllithium compounds are the most studied of alkali metal derivatives.^[1] Numerous anionic organosilicon compounds are

[*] Prof. Dr. A. Sekiguchi, Dipl.-Chem. T. Matsuno, Dr. M. Ichinohe
Department of Chemistry
University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)
Fax: (+81)298-53-4314
E-mail: sekiguch@staff.chem.tsukuba.ac.jp

[**] This work was supported by Grant-in-Aid for Scientific Research (Nos. 13029015, 13440185) from the Ministry of Education, Science and Culture of Japan, and TARA (Tsukuba Advanced Research Alliance) Fund.

known, however, knowledge of the chemistry of organosilicon compounds with an interaction between alkali metals and π electrons is very limited. To our knowledge, the only examples of such interactions are silole dianions $[\text{Li}(\text{thf})_2]\text{-}[\text{Li}(\text{thf})_3]\{\eta^1, \eta^5\text{-C}_4\text{Ph}_4\text{Si}\}$, $[\text{K}[18]\text{crown-6}]\{\eta^5, \eta^5\text{-C}_4\text{Me}_4\text{Si}\}$, and related compounds.^[2]

Recently, we synthesized the cyclotetrasilenylium ion ($\mathbf{1}^+\text{X}^-$),^[3] which is a free silyl cation in the condensed phase, by the reaction of cyclotrisilene $[(t\text{Bu}_2\text{MeSi})_4\text{Si}_3]$ ^[4] with $[\text{Et}_3\text{Si}(\text{C}_6\text{H}_5)]^+\text{X}^-$ ($\text{X}^- = \text{tetrakis(pentafluorophenyl)borate}$). We also reported the synthesis of the isolable cyclotetrasilenylium radical $\mathbf{1}^\bullet$ by the one-electron reduction of $\mathbf{1}^+\text{X}^-$.^[5] Therefore, it is reasonable to assume that the cyclotetrasilenylium ion $\mathbf{1}^+$ is formed by the two-electron reduction of $\mathbf{1}^+$ or one-electron reduction of $\mathbf{1}^\bullet$. A recent report by Weidenbruch and co-workers, on an unexpected formation of a cyclotetragermenylium derivative by the reaction of tetrakis(2,4,6-triisopropylphenyl)digermene with lithium in dimethoxyethane,^[6] prompts us to communicate our synthesis of the alkali metal derivatives of the cyclotetrasilenylium anion. We herein report the synthesis, characterization, and unique crystal structure of a cyclotetrasilenylium ($\mathbf{1}^+\text{Li}^+$), which has a π -type structure with coordination of a lithium cation to a trisilaallyl moiety. We also report a unique, reversible chemical redox system of the cyclotetrasilenylium cation, radical, and anion (Scheme 1).

The reaction of $\mathbf{1}^+\text{X}^-$ with an excess of lithium in oxygen-free, dry diethyl ether at room temperature lead to the immediate formation of a purplish red solution, caused by the formation of $\mathbf{1}^\bullet$. After about 30 min, the color of the solution changed to green, caused by the formation of 4,4-di-*tert*-butyl-1,2,3-tris(di-*tert*-butyl(methyl)silyl)cyclotetrasilenylium ($\mathbf{1}^-$) by further reduction. After removal of the excess lithium and the solvent, hexane was added to give green crystals of $\mathbf{1}^+\text{Li}^+$, which contained one equivalent of Et_2O , in 85% yield (Scheme 2). Reduction of $\mathbf{1}^\bullet$ with lithium in Et_2O at room

temperature also produced $\mathbf{1}^+\text{Li}^+$ cleanly. Compound $\mathbf{1}^+\text{X}^-$ also underwent two-electron reduction with sodium or potassium graphite (KC_8) in Et_2O , and the corresponding $\mathbf{1}^-\text{Na}^+$ and $\mathbf{1}^-\text{K}^+$ were obtained in 65% and 75% yields, respectively.

To determine the exact structure of $\mathbf{1}^+\text{Li}^+$ by X-ray crystallography, we performed a ligand exchange on the Li^+ ion, from Et_2O to tetrahydrofuran. A single crystal of $\mathbf{1}^+\text{Li}^+$, which contained one equivalent of THF, was obtained by recrystallization from a mixture of hexane and THF, the molecular structure was determined by X-ray crystallography (Figure 1).^[7] The lithium cation is located over the four-membered ring, and is coordinated by the three silicon atoms (Si1 , Si2 , and Si3) in the four-membered ring, as well as by the oxygen atom of the THF molecule.

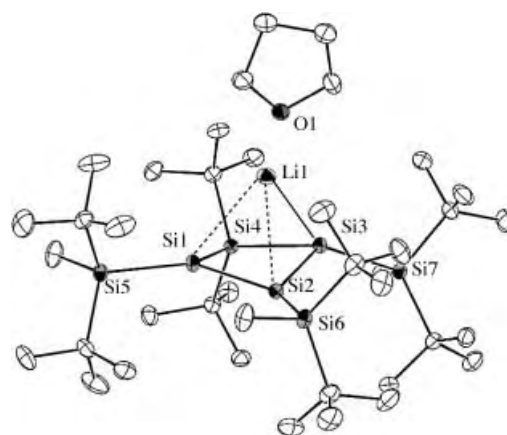
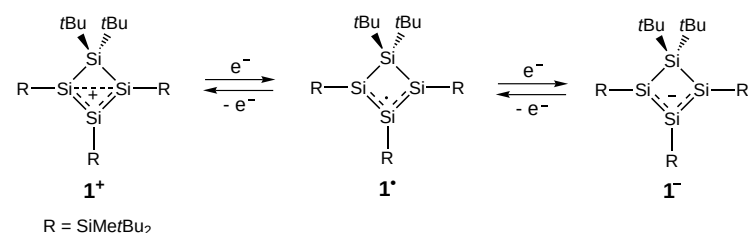
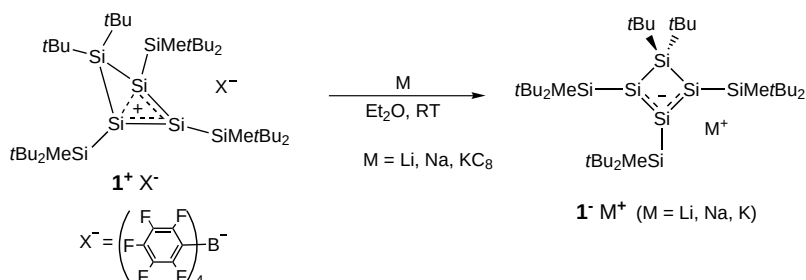


Figure 1. ORTEP representation of the structure of $\mathbf{1}^+[\text{Li}(\text{thf})]^+$ (hydrogen atoms are omitted for clarity; thermal ellipsoids set at the 30% level). Selected interatomic distances [Å] and angles [°]: Si1-Si2 2.2245(7), Si1-Si4 2.3692(7), Si1-Si5 2.3617(7), Si2-Si3 2.3153(7), Si2-Si6 2.4012(7), Si3-Si4 2.3955(7), Si3-Si7 2.3732(7), Si1-Li1 2.789(4), Si2-Li1 2.814(4), Si3-Li1 2.569(4); Si2-Si1-Si4 86.70(2), Si1-Si2-Si3 93.97(2), Si2-Si3-Si4 84.07(2), Si1-Si4-Si3 88.34(2).



Scheme 1.



Scheme 2. Reduction of $\mathbf{1}^+\text{X}^-$ with alkali metals.

The four-membered ring deviates from planarity, as demonstrated by the dihedral angle of 27.3° between the $\text{Si2-Si3-Si4/Si2-Si1-Si4}$ planes. The bond length of Si3-Li1 (2.569(4) Å) lies within the range for typical η^1 -type silyllithium compounds,^[1] whereas the bond lengths of Si1-Li1 (2.789(4) Å) and Si2-Li1 (2.814(4) Å) are significantly longer than that of Si3-Li1 (2.569(4) Å). The bond length of Si1-Si2 is 2.2245(7) Å, which lies in the reported range for Si=Si double bonds (2.138–2.289 Å).^[8] The bond lengths of Si2-Si3 (2.3153(7) Å) and Si1-Si4 (2.3692(7) Å) lie in the normal region for Si-Si single bonds (2.33–2.37 Å). These structural features suggest that $\mathbf{1}^+\text{Li}^+$ has a cyclotetrasilene structure with a Si=Si double bond in the ring, and that the lithium cation is bonded to the Si3 atom and also interacts with the double-bonded Si1 and Si2 atoms. Such an electrostatic interaction leads to elongation of the Si1-Si2 bond, which is intermediate between the Si=Si double bond (2.174(4) Å) and Si-Si single

bond (2.349(4)–2.450(4) Å) in the four-membered ring of hexakis(*tert*-butyldimethylsilyl)cyclotetrasilene.^[9, 10]

The NMR spectroscopic data of **1**[–]Li⁺ in [D₈]toluene indicate formation of a contact ion pair (CIP) with C₂ symmetry. The two *tert*-butyl groups that are attached to the Si4 atom show chemical shift nonequivalence, caused by coordination of the lithium cation (Figure 1). The two *tert*-butyl groups of *t*Bu₂MeSi that are attached to the Si1 and Si3 atoms are diastereotopic. Thus, the ¹H NMR spectrum of **1**[–]Li⁺ in [D₈]toluene reveals the presence of two methyl groups and five *tert*-butyl groups. The ¹³C NMR spectrum also shows signals arising from two methyl carbons for *t*BuMeSi, five methyl carbons for three *t*Bu₂MeSi and two *t*Bu groups, and five signals for quaternary carbon atoms of *t*Bu groups. In the ²⁹Si NMR spectrum, five signals are observed at δ = –31.5 (Si1 and Si3), 13.9 (Si6), 19.0 (Si5 and Si7), 26.0 (Si4), and 273.0 (Si2). The Si1 and Si3 atoms are equivalent, which indicates that the lithium cation is fluxional in solution, in accordance with an allylic-type anion. The signal appearing at δ = –31.5 is assigned to the Si1 and Si3 atoms, which are shifted upfield because of the negative charge. Of particular interest is the highly deshielded signal at δ = 273.0 arising from the Si2 atom, similar to the central carbon atom of allyllithium.^[11]

However, the Li⁺ ion can be separated from the anion to yield a solvent-separated ion pair (SSIP) in a solvating medium such as [D₈]THF. Consequently, the skeleton of **1**[–] has the same environment above and below the ring; the two *t*Bu groups attached to the Si4 atom are equivalent.^[12] The ¹H, ¹³C, and ²⁹Si NMR spectroscopic data of **1**[–]M⁺ (M = Li, Na, and K) in [D₈]THF all indicate SSIP formation in the polar solvent, caused by solvation of the counter cations.

The anion **1**[–] reacts readily with [Et₃Si(C₆H₅)]⁺X[–] in benzene to regenerate **1**[•]. The radical **1**[•] also undergoes one-electron oxidation to form **1**⁺ by the reaction of **1**[•] with [Ph₃C⁺]X[–] in benzene.^[5] Thus, we have prepared a reversible redox system of the cyclotetrasilenylium cation, radical, and anion.

Experimental Section

1[–]Li⁺: Crystals of **1**[–]X[–] (65 mg, 0.047 mmol) and lithium (18 mg, 2.6 mmol) were placed in a sealed tube with a magnetic stirrer bar. After degassing the tube, dry oxygen-free Et₂O (2.5 mL) was introduced by vacuum transfer and stirred at room temperature to give a green solution of **1**[–] within 1 h. After the solvent was removed in vacuo, degassed hexane was introduced by vacuum transfer. After the lithium and resulting X[–] salt had been removed from the tube, the solution was cooled to afford green crystals of **1**[–]Li⁺[(Et₂O)]⁺ (31 mg, 85%). ¹H NMR (300 MHz, [D₈]toluene, TMS): δ = 0.43 (s, 6H), 0.52 (s, 3H), 1.03 (t, *J* = 7.0 Hz, 6H), 1.21 (s, 18H), 1.26 (s, 18H), 1.28 (s, 18H), 1.42 (s, 9H), 1.75 (s, 9H), 3.39 (q, *J* = 7.0 Hz, 4H); ¹³C{¹H} NMR (100 MHz, [D₈]toluene, TMS): δ = –3.1 (CH₃), –1.5 (CH₃), 15.1 (CH₃CH₂O), 22.0 (C), 22.4 (C), 22.6 (C), 23.4 (C), 25.1 (C), 30.4 (CH₃), 30.71 (CH₃), 30.74 (CH₃), 31.2 (CH₃), 34.8 (CH₃), 66.3 (CH₃CH₂O); ²⁹Si{¹H} NMR (79.5 MHz, [D₈]toluene, TMS) δ = –31.5 (*2t*Bu₂MeSiSi), 13.9 (*t*Bu₂MeSi), 19.0 (*2t*Bu₂MeSi), 26.0 (*t*Bu₂Si), 273.0 (*t*Bu₂MeSiSi); ⁷Li{¹H} NMR (116.6 MHz, [D₈]toluene, LiCl in MeOH, external standard): δ = 1.96.

Received: December 17, 2001 [Z18402]

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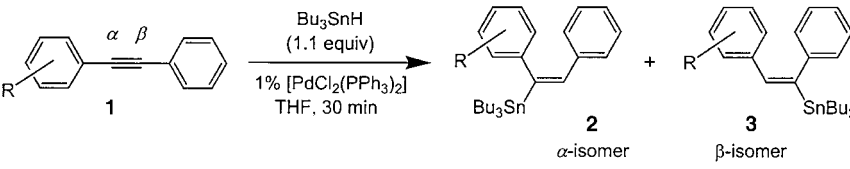
Ortho Substituents Direct Regioselective Addition of Tributyltin Hydride to Unsymmetrical Diaryl (or Heteroaryl) Alkynes: An Efficient Route to Stannylated Stilbene Derivatives**

Mouâd Alami,* Frédéric Liron, Marina Gervais, Jean-François Peyrat, and Jean-Daniel Brion

It is well known that the palladium-catalyzed hydrostannylation of internal alkynes proceeds in a stereoselective manner (*cis* addition) to yield vinyl stannanes.^[1] Regiochemical control of this reaction, nevertheless, remains a challenge, especially in the case of unsymmetrical disubstituted alkynes. In this respect, to our knowledge, hydrostannylation of alkynes with two different aromatic (or heteroaromatic) rings is not known.^[2] Herein, we describe the first highly regioselective Pd-catalyzed addition of tributyltin hydride to alkynes **1**, which is controlled by the *ortho* substituent at the aromatic ring, regardless of the electronic nature of this substituent. This reaction readily allows an efficient synthesis of stannylated, unsymmetrical 1,2-diaryl olefins **2**, which can be further transformed to variously substituted stilbenoid olefins. The latter are an interesting class of compounds, not only because of their occurrence as natural and biologically active substances,^[3] but also for their interesting physical properties.^[4]

Recently, we reported the effect of *ortho* substituents on the regioselectivity in the hydrostannylation of aryl-substituted alkynes.^[5] It then occurred to us that this unprecedented *ortho*-directing effect (ODE) could be extended to control the regiochemistry of the reaction of unsymmetrical diaryl (or heteroaryl) alkynes **1**. Initially, we examined the hydrostannylation of diaryl alkynes bearing a *para* π -electron-withdrawing group, which induces strong polarization of the carbon–carbon triple bond. Thus, reaction of **1a** with Bu₃SnH in the presence of 1% [PdCl₂(PPh₃)₂] in THF gave **2a** in 75% yield as a single isomer, through an exclusive *syn* addition (entry 1, Table 1). This regioselectivity is expected as the palladium-catalyzed hydrostannylation of electron-deficient alkynes formally proceeds by conjugate addition of the hydride.^[1c] In contrast to **1a**, hydrostannylation of diaryl alkyne derivatives **1b** and **1c**, which have a formyl or an

Table 1. Palladium-catalyzed hydrostannylation of unsymmetrical diaryl alkynes **1**.



Entry	R	2	Isolated yield [%]	3
1	a : <i>p</i> -NO ₂	75	— ^[a]	— ^[a]
2	b : <i>p</i> -CHO	—	98 ^[b]	—
3	c : <i>p</i> -CO ₂ Et	—	81 ^[b]	—
4	d : <i>p</i> -CH ₂ OH	—	86 ^[b]	—
5	e : <i>o</i> -CHO	95	— ^[a]	— ^[a]
6	f : <i>o</i> -CO ₂ Et	81	— ^[a]	— ^[a]
7	g : <i>o</i> -CH ₂ OH	95	— ^[a]	— ^[a]

[a] Stereoisomers **3** were not detected by ¹H NMR spectra in the crude reaction mixture. [b] Isolated yields of inseparable mixture of regioisomers. The ratios **2b**:**3b** 85:15, **2c**:**3c** 75:25 and **2d**:**3d** 50:50 were determined by ¹H NMR spectra in the crude reaction mixture.

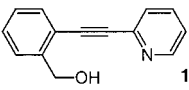
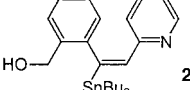
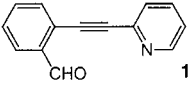
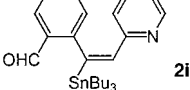
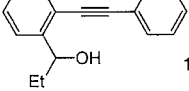
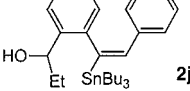
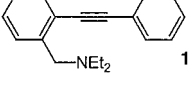
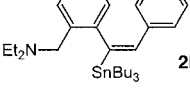
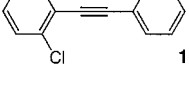
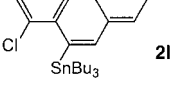
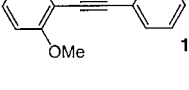
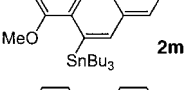
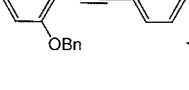
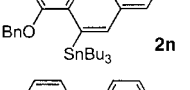
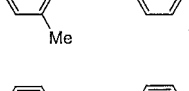
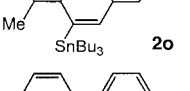
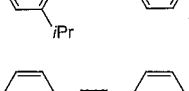
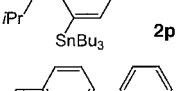
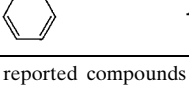
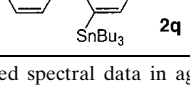
ethoxycarbonyl group (less powerful π -electron-withdrawing groups than the NO₂ moiety) in the *para*-position of the phenyl group, was less regioselective and gave a regioisomeric mixture with a preference for **2b–c** over **3b–c** (entries 2 and 3). In the case of alkyne **1d**, which contains a *para* σ -electron-donating group (R = *p*-CH₂OH, entry 4), the tributyltin hydride does not discriminate in its addition between the two carbon atoms of the triple bond, because the electronic effects of substituent groups through the aromatic ring appear to be minimal, and the reaction provided an inseparable 1:1 mixture of vinyl stannanes **2d** and **3d**. However, when the reaction was carried out with alkynes **1e–g**^[6] with an *ortho* substituent, regardless of the electronic nature of the substituent (π -electron-withdrawing group: entries 5 and 6, or σ -electron-donating group: entry 7) a total selectivity was obtained in favor of the α isomers **2e–g** (Bu₃Sn group being α relative to the *ortho*-substituted aryl moiety, selectivity α : β = 100:0, entries 5, 6, and 7). Stereoisomers **3e–g** were not detected by ¹H NMR analysis in the crude reaction mixture. From alkynes **1e** and **1f**, a reasonable explanation of the remarkable level of regioselectivity lies in the electronic effects of *ortho* π -electron-withdrawing groups together with a possible intramolecular chelation between the palladium center and the heteroatom. However, the result obtained from alkyne **1g** with an *ortho* σ -electron-donating group strongly indicates that this α selectivity could not be controlled by the electronic effects of substituents.

Hydrostannylation of various unsymmetrical *ortho*-substituted diaryl alkynes, as well as of alkynes bearing a pyridyl moiety, was examined (Table 2). Total regioselectivity toward the formation of the α isomers **2** was obtained from diaryl (or heteroaryl) alkynes **1h–l** (entries 1 to 5, Table 2) bearing an *ortho* benzylic substituent with a heteroatom or an *ortho* halide substituent, except in the case of **1m** where small amounts of β isomer **3m** were formed (R = *o*-OMe, α : β 90:10, entry 6).^[10] It is worth noting that the presence of an *ortho* benzylic substituent with a heteroatom or an *ortho* halide substituent on the aryl ring is not crucial to obtain regioselective addition of Bu₃SnH. Thus, hydrostannylation of **1o**, which bears an *ortho* methyl substituent, resulted mainly in

[*] Dr. M. Alami, F. Liron, M. Gervais, Dr. J.-F. Peyrat, Prof. Dr. J.-D. Brion
BioCIS
Laboratoire de Chimie Thérapeutique CNRS UPRES-A 8076
Université Paris XI, Faculté de Pharmacie
rue J.B. Clément, 92296 Châtenay Malabry Cedex (France)
Fax: (+33)1-4683-5828
E-mail: mouad.alami@cep.u-psud.fr

[**] ADIR (Servier Group) is gratefully acknowledged for a doctoral fellowship to M.G. We also thank the CNRS for support of this research and M. Ourevitch for the NMR analysis.

Table 2. Synthesis of various stannylated stilbene derivatives and related compounds.^[a]

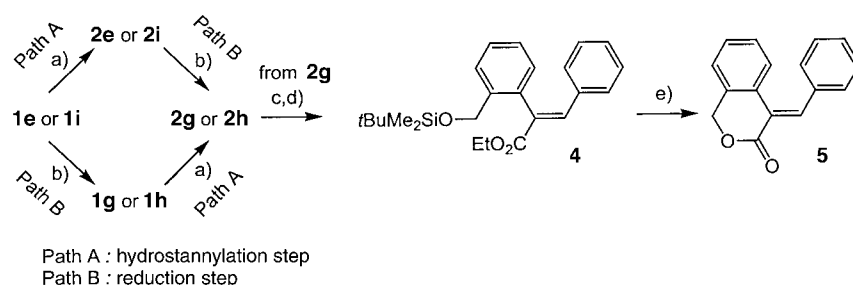
Entry	Diaryl alkyne ^[b] 1	Vinyl stannane ^[c] 2	Yield ^[d] [%]
1			81
2			90
3			91
4			60
5			85
6			94 ^[e]
7			81
8			91 ^[e]
9			76
10			67

[a] All the reported compounds exhibited spectral data in agreement with assigned structures. The regiochemistry of entries 4 and 8 was established by comparison of compounds **2k** and **2o** with samples obtained by the following sequence: 1) reaction of **2g** with CBr_4 , PPh_3 in CH_2Cl_2 followed by amination^[7] (Et_2NH , K_2CO_3 , KI, MeCN) of the corresponding bromide afforded **2k**. 2) Reduction of this bromide with NaBH_4 in DMSO^[8] led to **2o**. Regiochemical assignment of entry 3 was made as follows: **2j** showed the same ^1H NMR spectra with sample obtained by condensation of **2e** with EtMgBr . On the basis of these results, the regiochemistry shown was assumed for the products of entries 5–7, 9, and 10. [b] Diarylalkynes **1** were prepared according to ref. [9]. [c] All the compounds reported herein exhibited J values for the Sn–H coupling ranging from 60–70 Hz which are typical for *cis* configurations. [d] Yields are given for pure isolated products. [e] Isolated yields of inseparable mixture of regioisomers. Regioselectivity: **2m**:**3m** 90:10, **2o**:**3o** 93:7, as determined by ^1H NMR spectra of the crude reaction mixture.

the formation of the α adduct **2o** (α : β 93:7, entry 8), although no stabilizing effect can occur between the Pd atom and the methyl substituent. On the other hand, the reaction with the corresponding alkyne with a methyl group in the *para* position gives almost a 1:1 mixture of the two regioisomeric adducts. More interestingly, the presence of bulky substituents in the diaryl alkyne derivatives (**1n**: R = OBn, entry 7 or **1p**: R = *i*Pr, entry 9) does not affect the hydrostannylation reaction and gives α adducts **2n** and **2p** selectively, in good yields (76–81 %), without any β adduct. Finally, the addition of Bu_3SnH also proved to be regioselective with alkyne **1q**, in which the aromatic substituent on the triple bond is a 1-naphthyl group (entry 10).

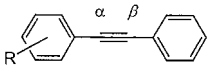
The regiochemical outcome for the selective formation of α adducts was established as follows. First, we showed that both sequences hydrostannylation–reduction (Path AB, Scheme 1) and reduction–hydrostannylation (Path BA, Scheme 1) of **1e** and **1i**, which have an *ortho* electron-withdrawing group, afforded the same α regioisomer **2g** and **2h**, respectively. Further evidence for the regioselectivity of compound **2g** was obtained by its conversion into 4-benzylidene-2-benzopyran-3-one **5** by an intramolecular lactonization of the ester **4**, which was readily obtained from **2g**, according to Scheme 1.

The results obtained in the case of *ortho*-substituted diaryl alkynes **1** show that the preferential attack of the tin atom occurs mainly and sometimes exclusively at the C_α atom, regardless of the electronic nature of the *ortho* substituent (compare hydrostannylation of **1e** and **f** with **1g**; Table 1 and **1h** with **1i**; Table 2). This ODE can not be explained by only chelation between the palladium atom and the group containing the heteroatom, because *ortho* alkyl derivatives exhibit very high selectivity (entries 8 and 9, Table 2). Moreover, our results also suggest that the reaction is not governed by steric effects, as an increase in the size of the *ortho* substituent resulted in an exclusive α selectivity (compare hydrostannylation of **1m** with **1n** entries 6 and 7, Table 2, and **1o** with **1p** entries 8 and 9, Table 2). There may be others factors in the reaction which account for the observed regiochemistry. We found that *ortho* substituents induced dramatic variations in the ^{13}C NMR chemical shifts of the triple bond.^[11] Table 3 summarizes the difference ($\Delta\delta_{\text{C}\beta-\text{C}\alpha}$) values found for the considered *ortho*- and *para*-substituted diaryl alkynes **1**. Thus, *ortho*-substituted alkynes



Scheme 1. Synthesis of tricycle **5**. Reagents and conditions: a) Bu_3SnH (1.1 equiv), $[\text{PdCl}_2(\text{PPh}_3)_2]$ (1 %), THF, 20 °C, 30 min (**2e**: 95 %, **2i**: 90 %, **2g**: 95 %, **2h**: 81 %); b) NaBH_4 , MeOH, –20 °C (**1g**: 74 %, **1h**: 70 %, **2g**: 67 %, **2h**: 78 %); c) $t\text{BuMe}_2\text{SiCl}$ (1.2 equiv), imidazole, DMF, 20 °C, 80 %; d) 1) $n\text{BuLi}$ (1.1 equiv), THF, –40 °C, 0.5 h; 2) $(\text{EtO})_2\text{CO}$, THF, –78 °C → 20 °C, 1 h, 57 %; e) $n\text{Bu}_4\text{NF}$ (1.2 equiv), THF, 0 ° → 20 °C, 60 %.

Table 3. Comparative chemical shifts (^{13}C NMR) of $\text{C}\equiv\text{C}$ in *ortho*- and *para*-substituted diaryl alkynes **1**.

Entry		Ratio ^[a] 2a:2b	^{13}C shifts ^[b] (± 0.05 ppm)		$\Delta\delta_{\text{C}\beta-\text{C}\alpha}$
			$\delta_{\text{C}\alpha}$	$\delta_{\text{C}\beta}$	
1	1s : R = <i>p</i> -Me	50:50	89.6	88.7	−0.9
2	1o : R = <i>o</i> -Me	93:7	88.6	93.6	5.0
3	1r : R = <i>p</i> -OMe	(40:60) ^[c]	89.4	88.1	−1.3
4	1m : R = <i>o</i> -OMe	90:10	85.7	93.4	7.7
5	1d : R = <i>p</i> -CH ₂ OH	50:50	89.7	89.4	−0.3
6	1g : R = <i>o</i> -CH ₂ OH	100:0	86.7	94.0	7.3
7	1c : R = <i>p</i> -CO ₂ Et	75:25	88.6	92.2	3.6
8	1f : R = <i>o</i> -CO ₂ Et	100:0	88.2	94.1	5.9
9	1b : R = <i>p</i> -CHO	85:15	88.5	93.3	4.8
10	1e : R = <i>o</i> -CHO	100:0	84.9	96.3	11.4

[a] Ratios were determined by ^1H NMR spectra of the crude reaction mixture. [b] Shifts are relative to external CDCl_3 . The assignment of the ^{13}C NMR chemical shifts of the triple bond was established by HMBC and HSQC NMR spectroscopy. [c] Interchangeable ratio.

1e and **1f**, in comparison to the *para* derivatives (**1b** and **1c**), showed that the presence of an *ortho* π -electron-withdrawing group induces strong electronic polarization of the carbon–carbon triple bond, which makes the C_β atom more electron positive and the C_α atom more electron negative (i.e. the signal arising from the C_β atom is 3.0 ppm upfield and the signal from the C_α atom is 3.6 ppm downfield when **1b** and **1e** are compared). More interestingly, for alkynes **1g**, **1m**, and **1o** in comparison with the *para* derivatives (**1d**, **1r**, and **1s**), the presence of an *ortho* σ -electron-donating group induced an inversion of the polarization of the carbon–carbon triple bond (the C_α atom becomes more electron rich than the C_β atom). This is illustrated by the change of sign of $\Delta\delta_{\text{C}\beta-\text{C}\alpha}$ values in *ortho*-substituted alkynes, which becomes positive rather than negative in the *para* derivatives. In Table 3, the presence of a methyl substituent in the *ortho* position increases the difference in the ^{13}C NMR chemical shift of the signals arising from the $\Delta\delta_{\text{C}\beta-\text{C}\alpha}$ atom from −0.9 ppm (for the $\Delta\delta_{\text{C}}$ atom of the *para*-substituted aryl alkyne **1s**) to 5.0 ppm (**1o**; entries 1 and 2, Table 3). A similar situation was noted when comparing various *ortho*- and *para*-substituted diaryl alkynes **1** (Table 3). We believe that this electronic polarization may be responsible for the remarkable regioselectivity observed, and therefore the hydride (H-PdSnBu_3) preferentially adds to the more electron-deficient terminus of the alkyne. To our knowledge, this reflection of the electronic effect of *ortho* substituents across the triple bond in the ^{13}C NMR spectra has never been reported.

In summary, we have demonstrated, for the first time, that a wide variety of unsymmetrical diaryl alkynes can undergo regioselective hydrostannylation when the diaryl alkyne is *ortho* substituted, regardless of the electronic nature of the substituent. Additionally, we showed for the first time that this *ortho* substituent induced dramatic electronic polarization of the carbon–carbon triple bond of the diaryl alkyne, which was presumably responsible for the α regioselectivity observed. The synthetic methodology described not only provides an easy access to stannylated-stilbene derivatives that are not easily prepared by other routes, but also will open up significant possibilities for performing various regioselective hydro- and carbo-metallation reactions of unsymmetrical diaryl (or heteroaryl) alkynes.

Experimental Section

2g: Tributyltin hydride (11 mmol, 2.95 mL) was added dropwise at room temperature to a solution of $[\text{PdCl}_2(\text{PPh}_3)_2]$ (0.1 mmol, 71 mg) and alkyne **1g** (10 mmol, 2.08 g) in THF (15 mL). The dark brown reaction mixture was stirred for an additional 15 min and then concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether:AcOEt 80:20) gave 4.74 g (95%) of pure **2g**. ^1H NMR (270 MHz, CDCl_3): δ = 7.31 (d, 1H, J = 7.6 Hz), 7.19 to 6.84 (m, 8H), 6.63 (s, 1H, $J_{\text{H-Sn}}$ = 65 Hz), 1.47 to 1.11 (m, 13H), 0.96 to 0.71 (m, 15H); ^{13}C NMR (67.5 MHz, CDCl_3): δ = 148.7, 143.6, 138.9, 137.1, 134.9, 128.6, 128.2, 127.9, 127.8, 127.1, 126.0, 125.6, 63.2, 28.2, 27.3, 13.6, 10.2.

Received: December 10, 2001 [Z18354]

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Evaluation of Diene Hierarchies for Diels–Alder Reactions En Route to Xestocyclamine A: Elaboration of an Ansa Bridge by *B*-Alkyl Suzuki Macrocyclization**

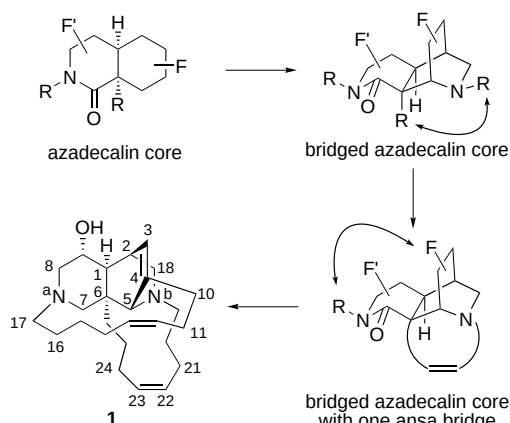
Alexandre Gagnon and Samuel J. Danishefsky*

Xestocyclamine A (**1**), a polycyclic alkaloid isolated from *Xestospongia* sp. (a marine sponge collected from the Milne Bay province of Papua, New Guinea)^[1] is an inhibitor of PKC β (PKC=protein kinase C).^[2] Compounds that exhibit this type of activity are of biomedical interest. They may be used, in principle, to intervene in a precise manner in the complex chemistry-based communication network that governs the life of a cell through signal transduction.^[3] The long-term hope, not yet demonstrated, is that of using specific PKC-directed agents as drugs in the treatment of cancer or other diseases of established mechanism.^[4]

In terms of its molecular architecture, xestocyclamine A (**1**) belongs to a broad family of natural products that share a common biogenetic motif.^[5] The group includes the manzamines,^[6a] the keramiphidins,^[6b] the halicyclamines,^[6c] the haliclamines,^[6d] the ingenamines,^[6e] and the ingamines.^[6f] From the perspective of the science of synthesis,^[7] xestocyclamine presents challenges of some moment. One soon takes note of its interesting 1,4-ethylene-bridged 2,7-diazadecalin matrix, which is further enveloped by two ansa bridges that connect N^a with C4 and N^b with C6 (Scheme 1). Herein, we report on progress directed to reaching xestocyclamine by total synthesis.

While a variety of options for progressing toward our goal merited consideration, we were particularly disposed toward routes that would make recourse to the *B*-alkyl Suzuki reaction (see below)^[8] for the establishment of one or even both ansa bridges. In our judgment, this method can fill an important niche in the establishment of olefinic linkages in complex structures with high stereocontrol. We viewed the xestocyclamine project as providing an opportunity to learn more about the reach of the *B*-alkyl Suzuki reaction in organic synthesis.

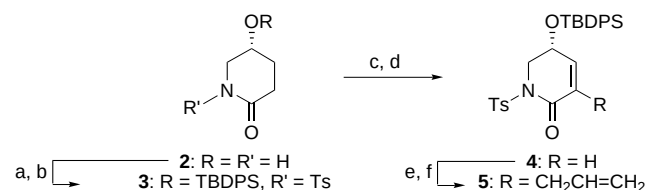
The matrix of xestocyclamine A consists of an azadecalin moiety with an additional aminomethylene bridge that joins C2 and C5. We first concerned ourselves with building this matrix in a concise way. Once the core was synthesized, we would address the matter of inserting the aminomethylene-



Scheme 1. Strategy for the synthesis of Xestocyclamine A. F, F' = unspecified functionality.

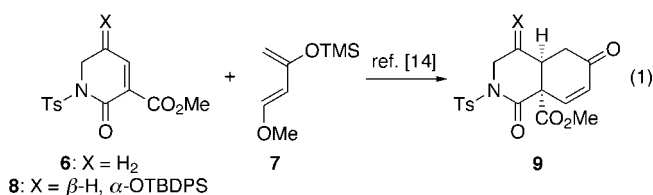
based bridge (Scheme 1). Both these subgoals would be attained in a way that allowed the ansa bridges to be stitched together.

The synthesis commenced with the conversion of the known enantiomerically pure (*R*)-5-hydroxy-2-oxopiperidine (**2**)^[9] into its derivative **3** (Scheme 2). The introduction of a dienophilic double bond into system **3** became the next subgoal. Phenylselenenylation of **3** followed by oxidative elimination gave **4**.^[10] Precedented iodination^[11] followed by Stille coupling^[12] allowed the smooth conversion of **4** into **5**. We hoped to establish the *cis*-fused azadecalin matrix with a Diels–Alder reaction by using dienophile **5**.



Scheme 2. Reagents and Conditions : a) TBDPSCl, imidazole, DMF, room temperature, 100 %; b) *n*BuLi, THF, 0 °C, then TsCl, DMAP, 0 °C → RT, 84 %; c) LDA, THF, –78 °C, then PhSeCl, –50 °C, 65 %; d) *m*CPBA, CH₂Cl₂, 85 %; e) I₂, pyridine, CCl₄, room temperature, 93 %; f) 3-iodoprop-1-ene, Cl₂Pd(PPh₃)₂, toluene, reflux, 69 %. TBDPS = *tert*-butyldiphenylsilyl; DMF = *N,N*-dimethylformamide; Ts = *para*-toluenesulfonyl; DMAP = 4-*N,N*-dimethylaminopyridine; LDA = lithium diisopropylamide; *m*CPBA = *meta*-chloroperoxybenzoic acid; PMB = *para*-methoxybenzyl.

It is necessary to digress briefly to set our study in its appropriate context. We recall two relevant instances from the literature in which a 3-substituted 5,6-dihydro- α -pyridone functioned as a dienophile in cycloadditions with 1,3-dioxygenated dienes. Thus, dienophile **6**, which has an activating carbomethoxy group at C3 of the dihydropyridone, reacts with diene **7**^[13] (which we introduced in 1974) in refluxing benzene to give **9** in moderate yield. Similarly, dienophile **8**, which has an additional γ -siloxy group, also undergoes cycloaddition, albeit in a lower yield [Eq. (1)].^[14]



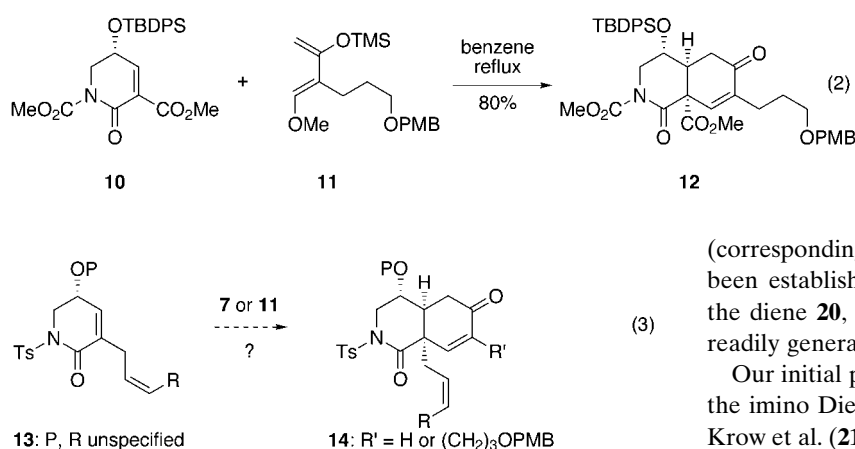
[*] Prof. S. J. Danishefsky, Dr. A. Gagnon
Department of Chemistry, Columbia University
Havemeyer Hall, New York, New York, 10027 (USA)
E-mail: s-danishefsky@ski.mskcc.org

Prof. S. J. Danishefsky
Laboratory for Bioorganic Chemistry
Sloan–Kettering Institute for Cancer Research
1275 York Avenue, Box 106, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691

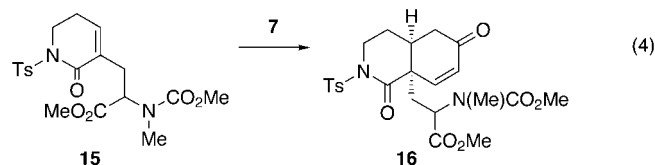
[**] This work was supported by the National Institutes of Health (Grant Number: HL25848). NSERC (Canada) Postdoctoral Fellowship support is gratefully acknowledged by A.G. We would like to thank Mr. David Churchill and Professor Gerard Parkin of Columbia University, NY for solving the X-ray crystal structure of **27** and **31**, and Dr. Yashuiro Itagaki for high-resolution mass-spectral analysis. A.G. would like to thank Dr. Sherry R. Chemler of the Sloan–Kettering Institute for Cancer Research for helpful discussions on the *B*-alkyl Suzuki reaction.

Indeed, an earlier foray of our laboratory directed at xestocylamine, commenced with a Diels–Alder reaction of dienophile **10** with diene **11** to give **12** [Eq. (2)].^[15] Although the carbomethoxy group undoubtedly activated the 5,6-dihydropyridone-based dienophile, we were unable to achieve reductive chain extension of the methyl ester grouping (corresponding to C26 of **1**).^[15]

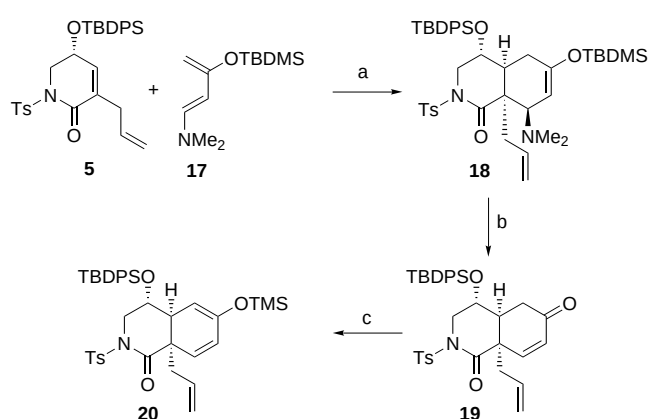
Based on these early experiments, we felt that to have a chance to eventually reach **1**, it would be critical to include an appropriate alkenyl group at C3 of the dienophile of the dihydropyridone (i.e. the carbon atom destined to become C6 of **1**). Accordingly, we sought to explore the value of **13** in this context. It was clear that **13** would not be as active as **10** in terms of its dienophilicity.^[16] However, a compound such as **14** (P, R = unspecified), which has an angular alkenyl, would be a suitable precursor for our target [Eq. (3)].



An encouraging precedent that showed that the Diels–Alder cycloaddition (even with a dienophile of type **13**) might be viable for our work was reported by Nakagawa and co-workers, who demonstrated that **15** does, in fact, undergo cycloaddition with diene **7** [Eq. (4)].^[17] Although this reaction gave a disappointing yield, we felt that the allyl group in our projected substrate **13** would be less deactivating to Diels–Alder reaction than the branched, highly substituted alanyl derivative at C3 in **15**.



We were therefore quite surprised that **5** did not undergo cycloaddition with either diene **7**^[13] or diene **11** under a variety of forcing conditions. We suspect that **5** (**13**) is less reactive than **15** because of the deactivating effect of the highly hindered electron-withdrawing siloxy group at C5.^[18] We therefore turned to the use of the Rawal–Kozmin diene (**17**)^[19] for cycloaddition with **5** (Scheme 3). Previous

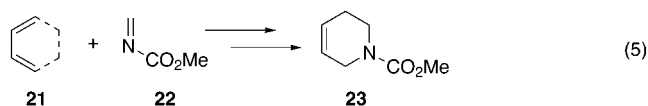


Scheme 3. Reagents and Conditions : a) benzene, reflux, 98%; b) HCl (aq., 2.1N), THF, room temperature, 76%; c) Et₃N, TMSOTf, CH₂Cl₂, 0 °C, 100%. TMSOTf = trimethylsilyl trifluoromethanesulfonate; TBDMS = *tert*-butyldimethylsilyl.

experiments from Rawal and co-workers had shown that **17** is more reactive than **7** in Diels–Alder reactions.^[20] Happily, cycloaddition did occur in refluxing benzene to afford exclusively the *endo* adduct **18**, which was treated with acid to afford **19**.

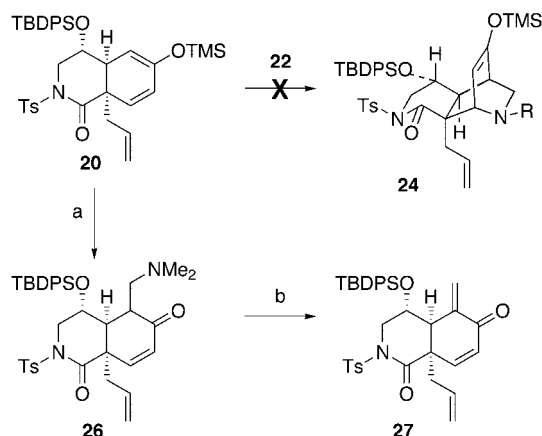
Thus, the three critical stereogenic centers (corresponding to C9, C1, and C6 of the target structure) had been established in enantiomerically pure form. Moreover, the diene **20**, projected for the next cycloaddition, could be readily generated.

Our initial plan to advance from **20** involved a variation of the imino Diels–Alder reaction reported by Cava et al. and Krow et al. (**21** + **22** → **23**) [Eq. (5)].^[21] Unfortunately, several



attempts at the cycloaddition of **20** with **22** (generated in situ) did not give rise to **24**. A key reaction for the carbon–carbon bond formation at the future C2 involved a method that we introduced in 1976.^[22] Reaction of **20** with Eschenmoser's salt (CH₂NMe₂I, **25**)^[23] did occur at room temperature (Scheme 4). Attempts to purify the presumed adduct **26** by silica-gel chromatography led to α -methyleneketone **27**. In the long term, it may well be possible to realize the proposed Diels–Alder reaction by fine-tuning the resident groups on the diene and on the azadienophile. However, we decided to proceed via **27**.

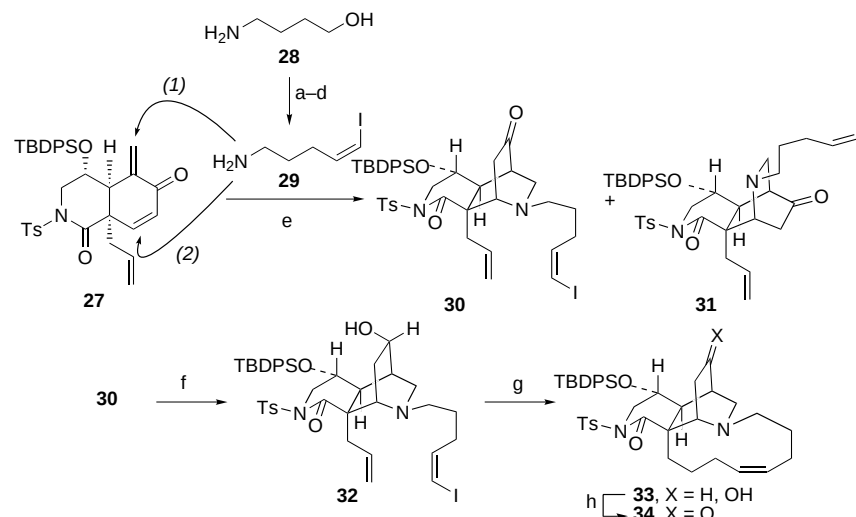
For this purpose, the commercially available amino alcohol **28** was converted in a series of straightforward steps into **29**. The *two* desired Michael additions^[24] of **29** to **27** (Scheme 5, (1) and (2)) afforded **30** (65%). Unfortunately, but not unexpectedly, the stereoisomeric isoquinulidone **31** was also formed (25%). Presumably, the formation of **30** and **31** reflects the lack of full α - or β -diastereofacial control in the proton transfer to C2 (with respect to **1**) in the intermolecular (first) Michael addition step, which joins **29** to



Scheme 4. Reagents and Conditions: a) $\text{CH}_2\text{NMe}_2\text{I}$ (**25**), CH_2Cl_2 ; b) SiO_2 , 85% over 2 steps.

27. Reduction of the keto function of **30** occurred stereospecifically to produce **32**. The stage was now set to test the applicability of the *B*-alkyl Suzuki reaction to close the first ansa bridge. Regiospecific hydroboration of **32** at the terminal vinyl group and subsequent intramolecular coupling led to **33** (60%). The alcohol function was oxidized with Dess–Martin periodinane to provide **34**.^[25]

In summary, the appropriate sequencing of three classic reactions, that is, 1) a Diels–Alder cycloaddition (**5** + **17**),^[19, 20] 2) an enoxysilane version of the Mannich reaction (**20** → **26**),^[22] and 3) a bridging annulation comprised of two Michael additions (**27** + **29**),^[26] set the stage for the increasingly powerful *B*-alkyl Suzuki methodology for macrocyclization (**32** → **33**). To reach xestocyclamine A (**1**), another ansa bridge between C4 (with respect to **1**) and the nitrogen atom



Scheme 5. Reagents and Conditions: a) CbzCl , Et_3N , CH_2Cl_2 , 0°C → RT, 83%; b) ClCOCOCI , DMSO , Et_3N , CH_2Cl_2 , -60°C , 35%; c) $\text{Ph}_3\text{PCH}_2\text{I}_2$, NaHMDS , HMPA , THF , -78°C , 61% over 2 steps, 5.3:1.0; d) TMSI , MeCN , 0°C , 35%; e) aluminum oxide, weakly acidic, DMSO , room temperature, 5 d, 90%, 2.6:1.0; f) NaBH_4 , MeOH , 0°C , 100%; g) 1) 9-BBN, THF , room temperature; 2) H_2O , room temperature; 3) dilution with THF/DMF and slow transfer over Ti_2CO_3 , $\text{Pd}(\text{dppf})\text{Cl}_2$, AsPh_3 (syringe pump), 60%; h) DMP, 72%. Cbz = carbobenzyloxy; HMDS = bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide; DMSO = dimethyl sulfoxide; 9-BBN = 9-borabicyclo[3.3.1]nonane; $\text{Pd}(\text{dppf})\text{Cl}_2$ = [1,1'-bis(diphenylphosphanyl)ferrocene]dichloropalladium(II); DMP = Dess–Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one.

of the A ring must be formed. Moreover, a quality total synthesis will require greater stereochemical control in the formation of **30**. These aims are currently under investigation in our laboratory.

Received: January 16, 2002 [Z18532]

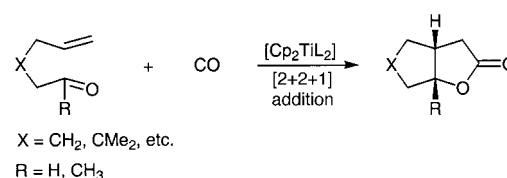
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- [16] Although quantitative data for this subject are not readily available, qualitatively, it is certain that the carbomethoxy group enhances the dienophilicity of a double bond much more than that of an allyl group; in fact, it is likely that the allyl group is more deactivating than H.
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Synthesis of α -Methylene- γ -butyrolactones: Ru-Catalyzed Cyclocarbonylation of Allenyl Aldehydes and Allenyl Ketones**

Suk-Ku Kang,* Kwang-Jin Kim, and Young-Taek Hong

Recently, Buchwald and co-workers^[1] as well as Crowe et al.^[2] independently described new titanium-mediated and -catalyzed hetero-Pauson–Khand reactions, which involved the $[2+2+1]$ cycloaddition of δ -unsaturated ketones and aldehydes with carbon monoxide to form fused bicyclic γ -butyrolactones (Scheme 1). Although titanium catalysis of



Scheme 1. $[2+2+1]$ Cycloaddition of δ -unsaturated ketones and aldehydes with CO to form fused bicyclic γ -butyrolactones. Ts = toluene-4-sulfonyl.

this process has proven to be efficient, the strength of the early transition metal–oxygen bond makes the catalytic sequence difficult when titanium reagents are used. A solution to this potential problem was provided by Murai and co-workers,^[3] who demonstrated that the late transition metal reagent $[\text{Ru}_3(\text{CO})_{12}]$ smoothly catalyzes $[2+2+1]$ cycloadditions of substituted δ -alkynyl aldehydes, with carbon monoxide to form fused α,β -unsaturated γ -butyrolactones.

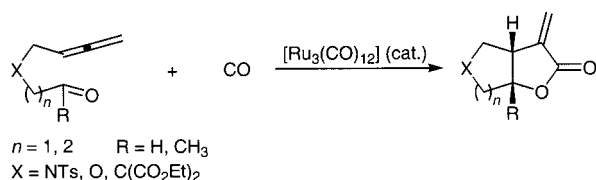
To the best of our knowledge, late transition metal catalyzed hetero-Pauson–Khand reactions of simple allenyl aldehydes and ketones have not yet been reported. Furthermore, this methodology has not been applied to the synthesis of α -methylene- γ -butyrolactones, a ring system found in numerous, biologically active natural products.^[4, 5] Hetero-Pauson–Khand carbonylative cyclizations of δ -allenyl aldehydes and ketones would serve as a direct entry into this family of compounds. We describe herein the preliminary results of an investigation into the latter and demonstrate that ruthenium-catalyzed $[2+2+1]$ cycloadditions of allenyl aldehydes and ketones with carbon monoxide serve as an efficient and direct route to α -methylene- γ -butyrolactones (Scheme 2).^[6–8]

[*] Prof. Dr. S.-K. Kang, K.-J. Kim, Y.-T. Hong
Department of Chemistry
and Laboratory for Metal-Catalyzed Reactions
Sungkyunkwan University
Suwon 440-746 (Korea)
Fax: (+82) 31-290-7079
E-mail: skkang@chem.skku.ac.kr

[**] This work was supported by the National Research Laboratory Project administrated by the Ministry of Science and Technology, KOSEF-CMDS, and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ2-PG6-01NA01-0002). We thank Professor Yoongho Lim (Konkuk University) for the NMR spectroscopic studies. K.-J.K. and Y.-T.H. are grateful for financial support from the BK21 program.



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Scheme 2. Ru-catalyzed [2 + 2 + 1] cycloadditions of allenyl aldehydes and ketones with CO to form α -methylene- γ -butyrolactones.

δ -Allenyl aldehyde **1a**^[9] was used to evaluate the feasibility of and to find optimal conditions for the α -methylene- γ -butyrolactone-forming cycloaddition process. Exploratory studies with this substrate showed that a variety of ruthenium reagents serve as effective catalysts for the conversion of **1a** into butyrolactone **2** (Table 1, entry 1). Among $[Ru_3(CO)_{12}]$, $[RuCl_2(CO)_2]$, $[RuCl_2(PPh_3)_3]$, and $[Cp_2Ru]$, the best catalyst for this process is $[Ru_3(CO)_{12}]$. Furthermore, dioxane was found to be superior to either toluene or *N,N*-dimethylformamide (DMF) as a solvent for this reaction. Thus, the optimum reaction conditions (75 % yield) for cyclocarbonylation of **1a** involves $[Ru_3(CO)_{12}]$ (1 mol %) in dioxane under CO (20 atm) at 120 °C for 12 h. The *cis* ring-fusion stereochemistry in **2a** was determined by using 2D-NOESY techniques in conjunction with molecular modeling (see Supporting Information).

The results presented in Table 1 demonstrate the generality of the α -methylene- γ -butyrolactone-forming, ruthenium-catalyzed carbonylative cycloaddition process. Importantly, under the reaction conditions described above, the δ -allenyl ketone **1d** affords the methyl-substituted *cis*- γ -butyrolactone **2d** in 82 % yield (Table 1, entry 4). The *cis* ring-fusion stereochemistry in **2d** was unambiguously assigned by using

Table 1. $[Ru_3(CO)_{12}]$ -catalyzed cycloaddition of allenyl aldehydes and allenyl ketones with CO.^[a]

Entry	Substrate	Product	Yield [%]
1			75
2			70
3			60
4			82 ^[b]
5			58 ^[b]

[a] The reactions were carried out with $[Ru_3(CO)_{12}]$ (1 mol %) and allenyl aldehyde or ketone **1** (1.0 equiv) in dioxane under CO (20 atm) at 120 °C for 12 h. [b] For 17 h. *t*Boc = *tert*-butoxycarbonyl.

NOE methods (methyl and ring-junction hydrogen atom). Likewise, the branched malonate **1e** was smoothly transformed into the *cis* lactone **2e** (Table 1, entry 5) under the ruthenium-catalyzed reaction conditions.

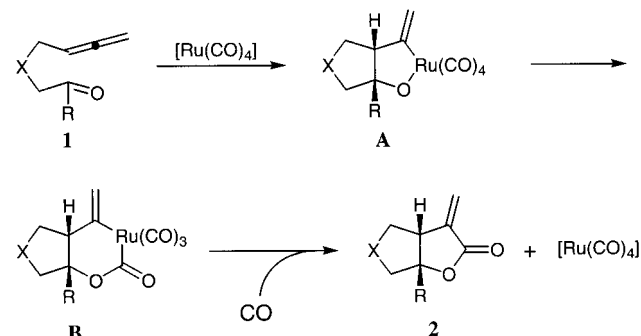
The cyclocarbonylation methodology is also applicable to the conversion of ϵ -allenyl aldehydes and ketones into the corresponding six-membered *cis* ring-fused α -methylene- γ -butyrolactones (Table 2). Notably, the ω -allenyl ketone **1j** afforded the methyl-substituted quaternary *cis*- γ -butyrolactone **2j** (Table 2, entry 5).

Table 2. $[Ru_3(CO)_{12}]$ -catalyzed cycloaddition of allenyl aldehydes and allenyl ketones with CO.^[a]

Entry	Substrate	Product	Yield [%]
1			60
2			72
3			61
4			55
5			48 ^[b]

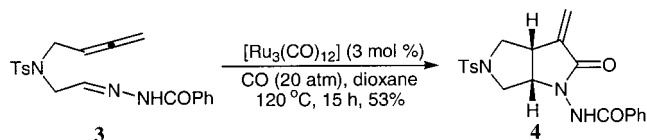
[a] The reactions were carried out with $[Ru_3(CO)_{12}]$ (1 mol %) and allenyl aldehyde or ketone **1** (1.0 equiv) in dioxane under CO (20 atm) at 120 °C for 12 h. [b] For 17 h.

The mechanistic pathway followed in this catalytic process most likely involves the intermediacy of metallacyclopentene **A** (Scheme 3), which undergoes insertion of CO to form the carbonylated metallacycle **B**. Reductive elimination then yields the bicyclic α -methylene- γ -butyrolactone product. In further studies to test this kind of cycloaddition in the formation ruthenacycle **A** with carbon monoxide to prepare



Scheme 3. Proposed mechanistic pathway for the Ru-catalyzed [2 + 2 + 1] cycloaddition.

fused α -methylene- γ -butyrolactam, we explored the cyclocarbonylation of δ -allenyl imine **3** and examined the stereochemistry of the resulting products (Scheme 4). We observed only the *cis*-fused α -methylene- γ -butyrolactam **4** as the sole product, which supports a [2 + 2 + 1] cycloaddition. The *cis* stereochemistry of **4** was clearly determined by NOE interactions in NOESY experiments (see Supporting Information).



Scheme 4. The cyclocarbonylation of δ -allenyl imine **3** gave *cis*-fused α -methylene- γ -butyrolactam **4** as the sole product.

In summary, the results presented above show that ruthenium-catalyzed cycloaddition reactions of allenyl aldehydes and ketones with carbon monoxide efficiently afford α -methylene- γ -butyrolactone products. This methodology should find wide applications in the synthesis of natural products that contain the *exo*-methylene- γ -butyrolactone functionality, and further investigations are underway in our laboratory.

Experimental Section

Typical procedure: A stainless-steel autoclave was charged with the allenyl aldehyde **1a** (80 mg, 0.30 mmol), 1,4-dioxane (4 mL), and $[\text{Ru}_3(\text{CO})_{12}]$ (2 mg, 1 mol %). The system was flushed three times with CO (20 atm). The autoclave was then pressurized to 20 atm, and the mixture was stirred at 120 °C for 12 h. The solution was then cooled and concentrated in vacuo to give a residue, which was subjected to silica-gel column chromatography (EtOAc/hexane 1:2) to yield the cyclized product **2a** (66 mg, 75%) as a white solid. M.p. 115 °C; R_f = 0.48 (EtOAc/hexanes 1:1); ^1H NMR (500 MHz, CDCl_3): δ = 2.45 (s, 3H), 3.07 (dd, 1H, J = 5.3, 11.7 Hz), 3.22 (dd, 1H, J = 10.0, 7.6 Hz), 3.37 (dd, 1H, J = 10.0, 2.9 Hz), 3.55 (m, 1H), 3.63 (dd, 1H, J = 0.6, 11.7 Hz), 4.97 (m, 1H), 5.77 (d, 1H, J = 2.4 Hz), 6.35 (d, 1H, J = 2.4 Hz), 7.36 (d, 2H, J = 8.2 Hz), 7.68 (d, 2H, J = 8.2 Hz); ^{13}C NMR (125 MHz, CDCl_3): δ = 169.6, 145.2, 137.4, 132.1, 130.6, 128.7, 125.8, 79.7, 55.2, 54.7, 42.6, 22.3; HR-MS: calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: 293.0776, found: 293.0705.

Typical experimental procedures for the preparation of **1a**, **1c–j**, **2a**, and **3**, as well as spectroscopic and analytical data for **1a–j**, **2a**, **2c–f**, **2i–j**, and **4** can be found in the Supporting Information.

Received: January 10, 2002 [Z18509]

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- [9] Preparation of allenyl aldehyde **1a**: a) propargyl *p*-tosylamide, $\text{BrCH}_2\text{CH}_2(\text{OMe})_2$, K_2CO_3 , DMF, 100 °C, 10 h, 85%; b) Crabbe reaction: HCHO , CuBr , $i\text{Pr}_3\text{NH}$, dioxane, reflux, 68% (see: F. Crabbe, B. Nassim, M.-T. Robert-Lopes, *Org. Synth. Coll. Vol. 7* (Ed.: J. P. Freeman), **1990**, pp 276–277); c) trifluoroacetic acid/ $\text{CHCl}_3/\text{H}_2\text{O}$ (1:2:1), 0 °C, 1.5 h, 78% (see Supporting Information).

Novel Ene-Like Cycloisomerization Reaction of Nitrile Oxides with a Tethered Allyltrimethylsilyl Group**

Teruhiko Ishikawa,* Jin Urano, Shushiro Ikeda, Yasuhiro Kobayashi, and Seiki Saito*

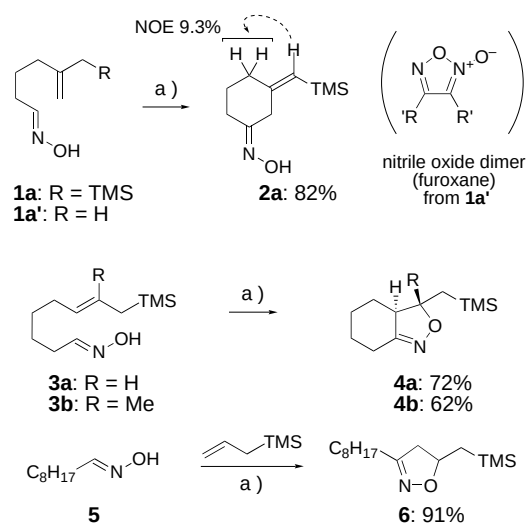
The nitrile oxide functional group is a well-known 1,3-dipole and highly useful owing to its high reactivity toward unsaturated C–C bonds to furnish [3+2] cycloadducts.^[1] In addition to such a traditional role, we have found that it also functions as an enophile^[2] in an intramolecular reaction with an allyltrimethylsilyl group.^[3] 5-Methylene-6-(trimethylsilyl)-hexanal oxime (**1a**) was treated with sodium hypochlorite^[4] in dichloromethane at 0 °C for 2 h to give the product of an ene-like reaction (**2a**) in 82% yield as a single diastereomer; no

[*] Dr. T. Ishikawa, Prof. S. Saito, J. Urano, S. Ikeda, Y. Kobayashi
Department of Bioscience and Biotechnology
Faculty of Engineering, Okayama University
Tsushima, Okayama, 700-8530 (Japan)
Fax: (+81)86-251-8209
E-mail: seisaito@biotech.okayama-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific research on Priority Areas (A) “Exploitation of Multi-Element Cyclic Molecules” from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

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[3+2] cycloadducts, fused or bridged, were detected (Scheme 1). In NMR experiments a distinct nuclear Overhauser enhancement (NOE) observed between the exocyclic olefinic proton and C(4) protons indicates their close proximity.



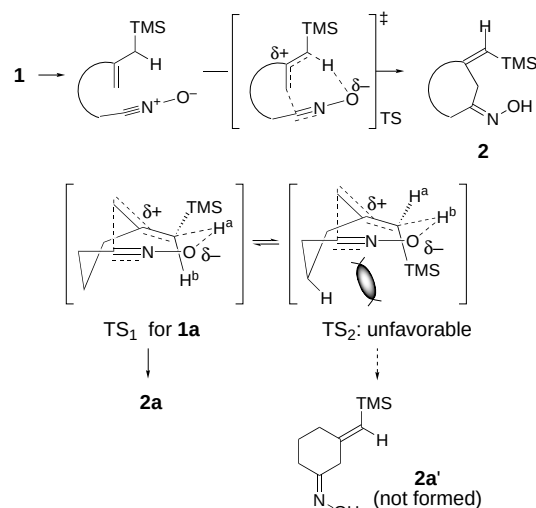
Scheme 1. Cycloisomerization reactions of **1** and [3+2] cycloaddition reactions of **3** and **5**. Conditions: a) NaOCl, CH₂Cl₂, 0 °C, 2 h. TMS = trimethylsilyl.

To our surprise, this novel reaction did not occur with substrates of similar structure such as **1a'**, **3a**, and **3b**, which instead underwent dimerization of nitrile oxide and expected [3+2] cycloaddition to give furoxane and isoxazolines (**4a** and **4b**), respectively (Scheme 1). Furthermore, no ene-like process was effected at all for the intermolecular version: the reaction of nonanal oxime **5** and allyltrimethylsilane afforded cycloadduct **6** almost quantitatively (Scheme 1).^[5]

This ene-like reaction is unprecedented^[6,7] and highly profitable because it features very mild reaction conditions (0 °C, 2 h), the formation of C–C bonds through a cycloisomerization process, and the retention of oxime and vinyltrimethylsilyl functions in the products, which would be suitable for further manipulations.

The selection of reaction pathways—the ene-like reaction or [3+2] cycloaddition—depends on whether the allyltrimethylsilyl unit is tethered to the oxime at the β -position (**1a**) or γ -position (**3a**, **3b**). Closely inspecting molecular models led us to speculate that **1a** is much more flexible than **3a** (or **3b**), which after deprotonation would lead to effective overlap of the π orbitals of the allyl sp² carbon atom and the nitrile oxide sp carbon atom. If this orbital overlap progresses at the transition state (Scheme 2, TS₁ for **1a**), proton delivery from the allylic position (H^a) to the negatively charged oxygen atom would be enhanced in a concerted manner and give rise to the cyclic oxime **2a** as a single isomer. The transition state leading to **2a'** (TS₂) is unfavorable because of inevitable steric interactions.

Although positive charge develops on the carbon β to the TMS group as the orbital overlap progresses at the transition state, it can be stabilized by the β -effect of the silicon atom.^[8] This is the reason why the allyltrimethylsilyl group is required



Scheme 2. Possible reaction mechanism of the novel cycloisomerization reaction.

for the ene-like reaction, and a simple allylic substrate **1a'** lacking the TMS group gave the nitrile oxide dimer (Scheme 1).

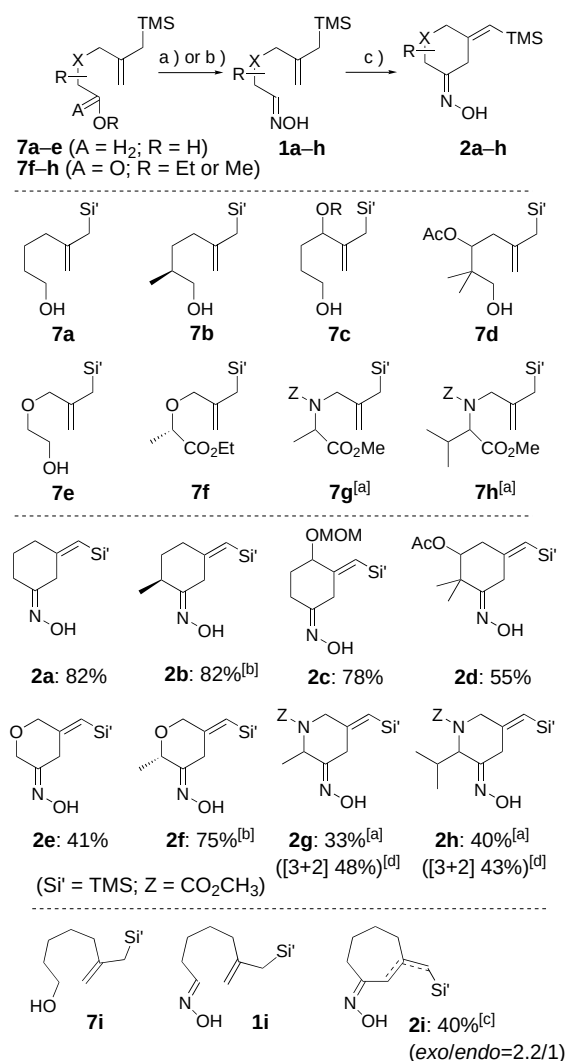
For this new C–C bond-forming process to be accepted as a general protocol in organic synthesis, simple and versatile methods for preparing **1** must be available. We have developed methods leading to key intermediate alcohols **7a–e** and esters **7f–h**,^[9] which are direct precursors for oximes **1a–h**, through oxidation and reduction, respectively, followed by condensation with hydroxylamine. These oximes underwent cycloisomerization under standard conditions to give the expected products **2a–h** (Scheme 3).

In every case a single geometrical isomer was obtained in moderate to high yields.^[10] NOE experiments revealed their geometries, which were additionally supported by the regio-specific Beckmann rearrangements of **2a** and **2b** to **8** and **9**, respectively (Scheme 4).^[11] Competitive ene-like reactions and intramolecular [3+2] cycloaddition reactions were observed for the aza versions **1g** and **1h** to give a mixture of cyclic oximes **2g** and **2h**, respectively, and isoxazolines (Scheme 3). Heptanal oxime **1i** proved to be amenable to the ene-like reaction to give cycloheptanone oxime **2i** in 40 % yield as a mixture of *exo* and *endo* isomers (bottom in Scheme 3).^[12]

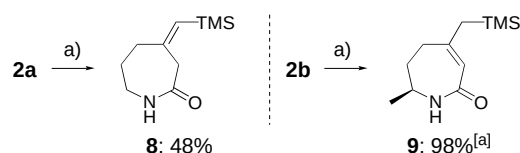
Although further studies are needed to completely understand the mechanism shown in Scheme 2, the potential intermediates **10** and **11** can be ruled out. Bredt's rule^[13] does not support the formation of the bridged [3+2] cycloadduct **10**. In addition, **10** and the cationic intermediate **11**, if produced, should afford possible geometrical isomer **2a'** and 3-(methylene)cyclohexanone oxime (**12**), which, in fact, were not detected at all (Scheme 5).

Experimental Section

General procedure for ene-like cyclizations: To a solution of oxime **1a** (70 mg, 0.36 mmol) in CH₂Cl₂ (7 mL) was slowly added an aqueous solution of NaOCl (available chlorine 5 %, 1.0 mL) at 0 °C over 1 h. The mixture was stirred vigorously and allowed to warm to room temperature for 1 h. The reaction mixture was diluted with water and extracted with several portions of EtOAc. The combined extracts were dried over Na₂SO₄

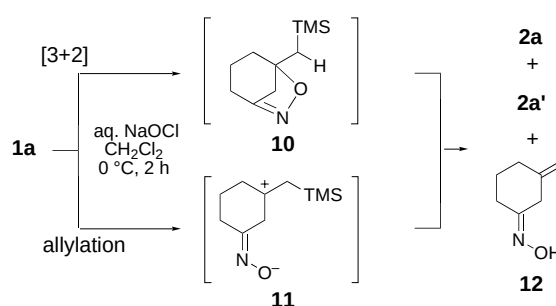


Scheme 3. Cycloisomerization reactions of various allylsilyl oximes. Yields are for products isolated by SiO₂ column chromatography in step c. Conditions: a) 1. SO₃ · pyridine, Et₃N/DMSO, 2. NH₂OH, Et₃N/EtOH; b) 1. DIBALH, THF, −78 °C, 1 h, 2. NH₂OH, Et₃N/EtOH; c) NaOCl/CH₂Cl₂, 0 °C → RT, 2 h. [a] Racemic product was obtained under the given conditions (see Supporting Information) though optically active amino acid esters were employed. [b] Optical purity, not determined. [c] Combined yield of *exo* and *endo* isomers, which could be separated by SiO₂ column chromatography. [d] For structures, see Supporting Information. DIBALH = diisobutylaluminum hydride, MOM = methoxymethyl.



Scheme 4. Synthesis of functionalized seven-membered lactams by the regioselective Beckmann rearrangement. Conditions: a) MsCl, pyridine/CH₂Cl₂, 0 °C, 2 h. [a] Optical purity, not determined. Ms = methane sulfonyl.

and concentrated to give an oil, which was purified by column chromatography on silica gel to afford the cyclic oxime **2a** (58 mg, 82 %).



Scheme 5. Hypothetical products via intermediates **10** and **11**.

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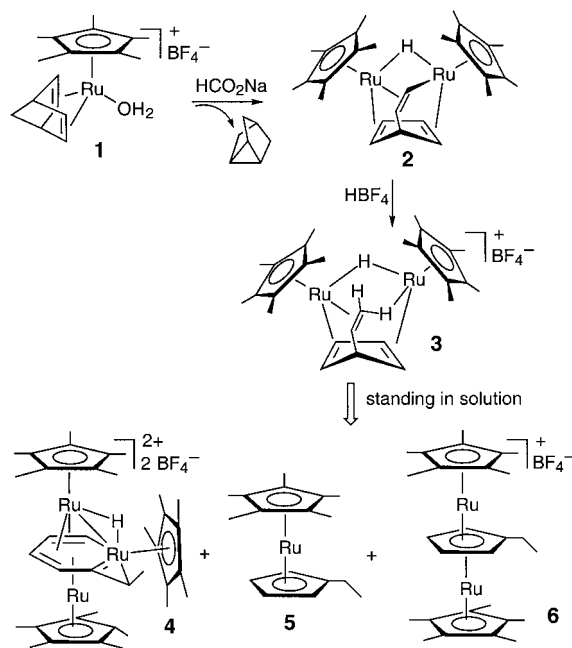
Received: September 21, 2001
Revised: February 4, 2002 [Z17943]

A Triple-Decker Complex with a Central Metallabenzene**

Sheng Hua Liu, Weng Sang Ng, Hei Shing Chu,
Ting Bin Wen, Haiping Xia, Zhong Yuan Zhou,
Chak Po Lau, and Guochen Jia*

It was established in the 1980s that benzene can act as a bridging ligand to form triple-decker complexes.^[1, 2] Recent studies on the chemistry of metallabenzenes revealed that transition metal containing metallabenzenes can display chemical properties similar to those of benzene.^[3] For example, they can undergo electrophilic substitution reactions^[4] and can form η^6 -metallabenzene complexes.^[5] These results imply that metallabenzenes may also function as bridging ligands in triple- or poly-decker complexes. However, such complexes have not yet been reported, although the possibility of obtaining triple-decker complexes with a central metallabenzene was suggested in 1994.^[5e] Here we describe the synthesis and characterization of the first triple-decker complex with a central metallabenzene.

Treatment of $[\text{Cp}^*\text{Ru}(\text{H}_2\text{O})(\text{nbd})]\text{BF}_4$ (**1**; $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$, nbd = norbornadiene)^[6] with HCO_2Na in dry THF produced the bimetallic complex **2** along with nortricyclene and a small amount of the known complex $[\text{Cp}^*\text{RuH}(\text{nbd})]$ (Scheme 1).^[7] Analytically pure samples of **2** were obtained by column chromatography. The structure of **2** was deduced on the basis of its mass spectrum and ^1H as well as $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic data. The ion peak at $m/z = 566$ corresponding to the composition $\{\text{Cp}_2^*\text{Ru}_2(\text{C}_7\text{H}_8)\}$ suggests that **2** is a bimetallic complex. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR data indicate that **2** is a fluxional hydride complex. The room-temperature ^1H NMR spectrum in C_6D_6 displayed a hydride signal at $\delta = -16.57$ and a broad Cp^* signal at $\delta = 1.88$. However, the ^1H NMR spectrum at 250 K in CD_2Cl_2 showed a sharp hydride signal at $\delta = -16.85$ and two Cp^* signals at $\delta = 1.77$ and 1.85, that is, the two Ru atoms in **2** are inequivalent at this temperature. The presence of the bridging C_7H_7 ligand is supported by its ^{13}C and ^1H NMR spectroscopic data. In particular, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum at 250 K in CD_2Cl_2 showed the signals of the α - and β -CH groups of the μ - σ , π -vinyl group at $\delta = 156.31$ and 60.84, respectively; that of the bridgehead CH group at $\delta = 47.02$; and those of the olefinic CH groups of the cyclopentadiene at $\delta = 26.24, 49.86, 58.86$, and 66.37. In the ^1H NMR spectrum, the signals of the α - and β -CH groups of the μ - σ , π -vinyl group were observed at $\delta = 5.94$ and 3.91, that of the bridgehead proton at $\delta = 3.47$, and



Scheme 1. Preparation of the triple-decker complex **4**.

those of the olefinic protons of the cyclopentadiene at $\delta = 1.82$ (1H), 2.59 (1H), and 2.65 (2H). The ^{13}C shift of $\delta = 156.31$ and the ^1H shift of $\delta = 5.94$ are comparable to those of the α -CH groups of other μ - σ , π -vinyl ligands.^[8] Although the detailed mechanism is not yet clear, the bridging ligand in **2** is apparently formed by C–C bond cleavage of a norbornadiene ligand. Cleavage of C–C bonds of norbornadiene by late transition metal complexes to give fulvene or vinylcyclopentadiene species has been reported.^[6, 7, 9]

Protonation of **2** with HBF_4 produced the bimetallic complex **3**, which was previously obtained by protonation of $[\text{Cp}^*\text{RuH}(\text{nbd})]$ with HBF_4 .^[7] In attempts to grow crystals of **3**, we found that the complex is unstable and was converted to other species in solution. When a solution of **3** in $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ was stored at room temperature for a week, a brown crystalline solid and a brown solution were produced. The solid was identified as the triple-decker complex **4**. From the solution, the ruthenocene **5** and the ethylcyclopentadienyl-bridged triple-decker complex **6** were isolated.

Complexes **5** and **6** were readily characterized by their MS and NMR spectroscopic data. For example, the CI-MS of **5** showed the molecular ion peak at $m/z = 330$ corresponding to the composition of $\{\text{Cp}^*\text{Ru}(\text{C}_7\text{H}_9)\}$. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of **5** displayed the characteristic signals of $\eta^5\text{-C}_5\text{Me}_5$ and $\eta^5\text{-C}_5\text{H}_4\text{Et}$. The ^1H NMR spectrum of **6** showed the Cp^* signal at $\delta = 1.93$, and the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **6** showed Cp^* signals at $\delta = 10.46$ and 86.49. The presence of bridging $\text{C}_5\text{H}_4\text{Et}$ in **6** is supported by the ^1H NMR spectrum (in CD_2Cl_2), which showed ethyl signals at $\delta = 1.23$ (CH_3) and $\delta = 2.63$ (CH_2) as well as C_5H_4 signals at $\delta = 4.12$ and 4.27. Consistent with the structure, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (in CD_2Cl_2) showed ethyl signals at $\delta = 10.94$ (CH_3) and 19.84 (CH_2) as well as C_5H_4 signals at $\delta = 55.17$ (CH), 56.29 (CH), and 76.20 (C). The bridging $\text{C}_5\text{H}_4\text{Et}$ ligand in **6** is presumably formed by insertion of the vinylcyclopentadiene ligand into the Ru–H bond of **3** followed by hydrogen shift. The first

[*] Prof. G. Jia, Dr. S. H. Liu, Dr. W. S. Ng, Dr. H. S. Chu, T. B. Wen, H. Xia
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon (Hong Kong)
Fax: (+852) 2358-1594
E-mail: chjiag@ust.hk

Prof. Z. Y. Zhou, Prof. C. P. Lau
Department of Applied Biology and Chemical Technology
Hong Kong Polytechnic University
Kowloon (Hong Kong)

[**] This work was supported by the Hong Kong Research Grant Council and The Hong Kong University of Science and Technology.

cyclopentadienyl-bridged triple-decker complex was discovered by Werner et al. about 30 years ago.^[10] Closely related ruthenium triple-decker complexes such as $[(\text{Cp}^*\text{Ru})_2(\mu\text{-C}_5\text{R}_5)]^+$ ($\text{R} = \text{H}, \text{Me}$) are known and were prepared by different routes.^[11]

The most interesting product is the triple-decker complex **4**, which contains a bridging metallabenzene. Its structure was established by X-ray diffraction (Figure 1).^[12] The complex

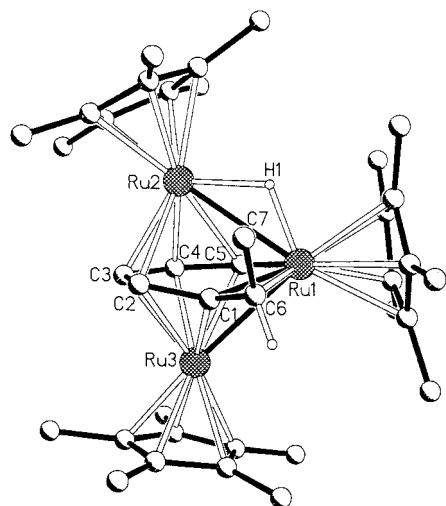


Figure 1. Molecular structure of **4**. Selected bond lengths [Å] and angles [°]: Ru1–Ru2 2.9065(9), Ru1–Ru3 2.9386(9), Ru1–C1 2.043(8), Ru1–C5 2.055(7), C1–C2 1.410(10), C2–C3 1.463(11), C3–C4 1.400(10), C4–C5 1.358(9), C1–C6 1.392(11), C6–C7 1.467(12), Ru1–C6 2.219(9), Ru1–H1 1.70(6), Ru2–H1 2.00(6), Ru2–C1 2.699(10), Ru2–C2 2.339(7), Ru2–C3 2.195(7), Ru2–C4 2.248(7), Ru2–C5 2.395(7), Ru3–C1 2.126(9), Ru3–C2 2.274(7), Ru3–C3 2.215(7), Ru3–C4 2.200(8), Ru3–C5 2.299(8); C1–Ru1–C5 82.2(3), C2–C1–Ru1 130.1(7), C3–C2–C1 120.4(7), C4–C3–C2 121.5(6), C5–C4–C3 125.0(7), C4–C5–Ru1 132.9(6), C1–Ru1–C6 37.8(3), C5–Ru1–C6 120.0(3), C2–C1–C6 139.6(8), C6–C1–Ru1 78.0(5), C1–C6–C7 121.5(9), C1–C6–Ru1 64.2(5), C7–C6–Ru1 121.0(7), Ru2–Ru1–Ru3 75.91(2).

contains a central six-membered metallacycle, which is η^6 -bonded to Ru3 with a Ru3–Ru1 distance of 2.9386(9) Å and an average Ru3–C distance of 2.223 Å. Except for C1, all the atoms of the central metallacycle are also bonded to Ru2, with an Ru2–Ru1 distance of 2.9065(9) Å and an average Ru2–C distance of 2.294 Å. The distance between Ru2 and C1 (2.699(10) Å) is too long for a normal covalent Ru–C bond. A hydrogen atom bridges Ru1 and Ru2. The Ru1–Ru2 and Ru3–Ru1 bond lengths are close to those of reported Ru–Ru single bonds.^[5a–d] The atoms Ru1 and C2–C5 are coplanar, with a maximum deviation from the least-squares plane of -0.0391 Å for C3. The atom C1 lies 0.3872 Å out of the plane and is tilted toward Ru3. The Ru1–C1 and Ru1–C5 bond lengths are essentially equal and are within the range of those reported for η^6 -ruthenabenzene.^[5a–d] As expected, the Ru1–C1 and Ru1–C5 bonds are shorter than the Ru1–C6 bond. There is no short–long bond alternation in the C1–C5 carbon chain. This structural feature indicates that the middle metallacycle has a delocalized electronic structure.

Consistent with the solid-state structure, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum showed three sets of Cp* signals. The ^{13}C signals of the bridging ligand were observed at $\delta = 24.36$ (C7), 37.42

(C2), 41.52 (C6), 54.02 (C4), 64.83 (C3), 146.89 (C5), and 168.32 (C1). In the ^1H NMR spectrum (in CD_2Cl_2), the hydride peak was observed at $\delta = -13.51$; the three Cp* signals (1:1:1 intensity) were located at $\delta = 1.91, 1.93$, and 2.39 ; and the signals of the bridging ligand appeared at $\delta = 1.40$ (CH₃), 4.06 (C6H), 5.26 (C2H), 5.46 (C4H), 7.13 (C3H), and 8.20 (C5H).

In the 30-valence-electron triple-decker complex $[(\eta^6\text{-mesitylene})\text{Cr}]_2(\mu\text{-}\eta^6\text{-mesitylene})$,^[1b] the central arene molecule is η^6 -bonded to both metal centers. The central metallabenzene in **4** is bonded η^5 to Ru2 and η^6 to Ru3. Such a structural feature is understandable, because the hydrido ligand bridging Ru1 and Ru2 allows Ru2 to attain 18 valence electrons without forming a bond to C1. “Slipped” triple-decker complexes were previously reported for electron-rich systems, for example, $[(\text{Cp}^*\text{Co})_2(\mu\text{-}(\eta^4\text{-}^i\text{-cumene}))]$,^[13a] $[(\eta^5\text{-C}_5\text{H}_2\text{tBu}_3\text{Co})_2(\mu\text{-}\eta^4\text{-}^i\text{-toluene}))]$,^[2b] $[(\text{CpRu})_2(\mu\text{-}\eta^5\text{-}\eta^5\text{-cot})]$,^[13b] $[(\text{CpRh})_2(\mu\text{-}\eta^5\text{-}\eta^5\text{-cot})](\text{PF}_6)_2$,^[13c] and $[(\eta^8\text{-cot})\text{Ti}]_2\text{-}[\mu\text{-}\eta^5\text{-}\eta^5\text{-cot}]$ (cot = 1,3,5,7-cyclooctatetraene).^[13d]

Complex **4** is the first well-characterized triple-decker complex with a bridging metallabenzene ligand. Triple-decker complexes with bridging benzene,^[1, 2] a heterobenzene containing a main group element (e.g., borabenzenes),^[14] and inorganic benzene analogues (e.g., P₆, metallaboranes)^[15] have all been made. Conversion of **3** to **4** is also interesting, as it involves C–C bond cleavage of vinylcyclopentadiene (formed from norbornadiene) under mild conditions. Metal-promoted C–C bond activation is of much current interest.^[16] Cleavage of a C–C bond of cyclopentadiene was observed in the reaction of cyclopentadiene with the trinuclear ruthenium cluster $[(\text{Cp}^*\text{Ru})_3(\mu\text{-H})_3(\mu_3\text{-H})_2]$.^[17] While this work was in progress, Suzuki et al. reported that reaction of $[(\text{Cp}^*\text{Ru})_2(\mu\text{-H})_4]$ with norbornadiene at 60 °C gives $[(\text{Cp}^*\text{Ru})_2(\mu\text{-}\eta^5\text{-}\eta^1\text{-}\eta^1\text{-C}_5\text{H}_4\text{CH}_2\text{CH}_3)(\text{H})]$.^[5d]

In summary, we have prepared the first triple-decker complex with a bridging metallabenzene by C–C bond activation of norbornadiene under mild conditions. We are currently studying the mechanism of these interesting transformations and preparing other triple-decker complexes with bridging metallabenzenes.

Experimental Section

2: A mixture of **1** (1.0 g, 2.3 mmol) and HCO_2Na (1.0 g, 15 mmol) in dry THF (50 mL) was stirred for 3 h. The solvent of the reaction mixture was evaporated to dryness. The residue was extracted with hexane (50 mL). The extract was concentrated to dryness, and the residue was purified by column chromatography (neutral alumina, eluent: benzene) to give **2** as a brown-yellow solid (0.48 g, 74 %). The formation of nortricyclicene in the reaction was confirmed by ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR experiments. ^1H NMR (300.13 MHz, CD_2Cl_2 , 250 K): $\delta = -16.85$ (s, 1H, Ru($\mu\text{-H}$)Ru), 1.77 (s, 15H, Cp*), 1.85 (s, 15H, Cp*), 1.82 (m, 1H, =CH), 2.59 (m, 1H, =CH), 2.65 (m, 2H, =CH), 3.47 (dt, $J(\text{H,H}) = 3.7, 4.6$ Hz, 1H, CH), 3.91 (dd, $J(\text{H,H}) = 3.7, 5.5$ Hz, 1H, =CH), 5.94 (d, $J(\text{H,H}) = 5.5$ Hz, 1H, =CHRu); ^1H NMR (300.13 MHz, C_6D_6 , 298 K): $\delta = -16.57$ (s, 1H, Ru($\mu\text{-H}$)Ru), 1.88 (br, 30H, Cp*), 2.05 (s, 1H, =CH), 3.02 (s, 3H, =CH), 3.86 (s, 1H, CH), 4.19 (s, 1H, =CH), 6.26 (d, $J(\text{H,H}) = 5.1$ Hz, 1H, =CHRu); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.48 MHz, CD_2Cl_2 , 250 K): $\delta = 10.24$ (s, Cp*), 10.35 (s, Cp*), 26.24 (s, =CH), 47.02 (s, CH), 49.86 (s, =CH), 58.86 (s, =CH), 60.84 (s, =CH), 66.37 (s, =CH), 89.54 (s, Cp*), 91.90 (s, Cp*), 156.31 (s, =CH–Ru); MS (FAB, NBA matrix): m/z (%): 566 (90) [M^+]; C,H analysis (%) calcd for $\text{C}_{27}\text{H}_{38}\text{Ru}_2$: C 57.42, H 6.78; found: C 57.26, H 6.63.

4–6: HBF₄·Et₂O (0.1 mL) was added to a solution of **2** (0.20 g, 0.35 mmol) in Et₂O (30 mL). The reaction mixture was stirred for 5 min to give an orange solid, which was collected by filtration, washed with Et₂O, and dried under vacuum to give **3** (0.15 g, 67%). Complex **3** (0.20 g, 0.31 mmol) was dissolved in CH₂Cl₂ (2 mL), which was then layered with diethyl ether (10 mL). The mixture was allowed to stand for a week to give a brown solution and brown-red needles of **4**, which were collected by filtration, washed with hexane (5 mL), and dried under vacuum (0.080 g, 40% based on Ru). The mother liquor was evaporated to dryness, and hexane (10 mL) was added to give a brown-yellow solid, which was collected by filtration, washed with hexane, and dried under vacuum to give **6** (0.076 g, 38% based on Ru). The filtrate was concentrated to dryness, and the residue purified by column chromatography (silica gel, eluent: hexane) to give **5** as a colorless oil (0.015 g, 8% based on Ru). **4**: ¹H NMR (300.13 MHz, [D₆]acetone): δ = −13.51 (d, J(H,H) = 1.38 Hz, 1H, RuH), 1.40 (d, J(H,H) = 5.37 Hz, 3H, CH₃), 1.91 (s, 15H, Cp*), 1.93 (s, 15H, Cp*), 2.39 (s, 15H, Cp*), 4.06 (qd, J(H,H) = 5.73, 1.38 Hz, 1H, Ru-CH-CH₃), 5.26 (d, J(H,H) = 5.37 Hz, 1H, =CH), 5.46 (dd, J(H,H) = 7.23, 4.95 Hz, 1H, =CH), 7.13 (t, J(H,H) = 5.13 Hz, 1H, =CH), 8.20 (d, J(H,H) = 7.23 Hz, 1H, =CH); ¹³C{¹H} NMR (75.48 MHz, [D₆]acetone): δ = 9.64 (s, Cp*), 9.75 (s, Cp*), 10.10 (s, Cp*), 24.36 (s, CH₃), 37.42 (s, =CH), 41.52 (s, RuCHCH₃), 54.02 (s, =CH), 64.83 (s, =CH), 92.48 (s, Cp*), 106.20 (s, 2 Cp*), 146.89 (s, =CHRu), 168.32 (s, =CRu); elemental analysis (%) calcd for C₃₇H₅₄B₂F₈Ru₃: C 45.55, H 5.58; found: C 45.80, H 5.62. **5**: ¹H NMR (300.13 MHz, CDCl₃): δ = 1.16 (t, J(H,H) = 7.5 Hz, 3H, CH₃), 1.99 (s, 15H, Cp*), 2.20 (q, J(H,H) = 7.5 Hz, 2H, CH₂), 4.15 (s, 4H, Cp); ¹³C{¹H} NMR (75.48 MHz, CDCl₃): δ = 11.74 (s, Cp*), 14.63 (s, CH₃), 20.81 (s, CH₂), 71.81 (s, Cp), 71.91 (s, Cp), 84.32 (s, Cp*), 92.13 (s, Cp); MS (CI): m/z (%): 330 (100) [M⁺]. **6**: ¹H NMR (300.13 MHz, CD₂Cl₂): δ = 1.23 (t, J(H,H) = 7.6 Hz, 3H, CH₃), 1.93 (s, 30H, Cp*), 2.63 (q, J(H,H) = 7.6 Hz, 2H, CH₂), 4.12 (s, 2H, Cp), 4.27 (s, 2H, Cp); ¹³C{¹H} NMR (75.48 MHz, CD₂Cl₂): δ = 10.46 (s, Cp*), 10.94 (s, CH₃), 19.84 (s, CH₂), 55.17 (s, Cp), 56.29 (s, Cp), 76.20 (s, Cp), 86.49 (s, Cp*); elemental analysis (%) calcd for C₂₇H₃₉BF₄Ru₂: C 49.70, H 6.02; found: C 50.02, H 5.86.

Received: November 6, 2001 [Z18172]

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β = 87.415(3), *γ* = 80.060(3)°, *V* = 1902.7(4) Å³; *Z* = 2, *ρ*_{calcd} = 1.703 g cm^{−3}; 12561 reflections, 8468 independent reflections (*R*_{int} = 0.0571); *R*₁ = 0.0560, *wR*₂ = 0.1104 for 527 parameters and 4100 reflections with *I* > 2σ(*I*). Crystals of **4** suitable for X-ray diffraction were grown from a solution in CH₂Cl₂ layered with diethyl ether. Intensity data were collected on a Bruker SMART CCD Area Detector with graphite-monochromated MoK α radiation at room temperature. The structure was solved by direct methods, expanded by difference Fourier syntheses, and refined by full-matrix least-squares methods on *F*² by using the Bruker SHELXTL (Version 5.10) program package. All non-hydrogen atoms were refined anisotropically. The two BF₄[−] counteranions were highly disordered, and their atomic distances (B–F, F...F) were constrained during the structural refinement. The metal-bound hydrido ligand H1 was located in the difference Fourier map and refined with isotropic thermal parameter. The remaining hydrogen atoms were placed in ideal positions and refined with a riding model. CCDC-173137 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Synthesis, Structure, and Molecular Orbital Calculations of Chromium(III) and Iron(III) Complexes Containing η²-Pyrazolato Ligands**

Karl R. Gust, John E. Knox, Mary Jane Heeg, H. Bernhard Schlegel, and Charles H. Winter*

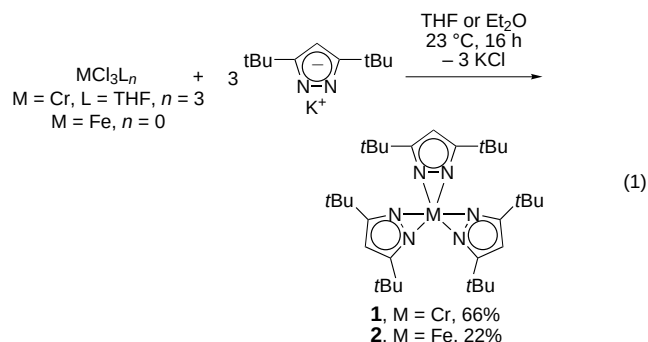
The coordination chemistry of pyrazolato ligands has been extensively explored, particularly among complexes of the mid to late transition metals.^[1] Among the 1656 Group 6–11 complexes containing pyrazolato ligands whose structures

[*] Prof. Dr. C. H. Winter, K. R. Gust, J. E. Knox, Dr. M. J. Heeg, Prof. Dr. H. B. Schlegel
Department of Chemistry
Wayne State University
Detroit, Michigan 48202 (USA)
Fax: (+1) 313-577-1377
E-mail: chw@chem.wayne.edu

[**] We thank the U.S. National Science Foundation for support of this research. We are grateful to Professor John McCracken of Michigan State University for assistance with the EPR measurements.

have been deposited in the Cambridge Crystallographic Database to date (version 5.21; April 2001), coordination modes have been limited to η^1 and $\mu\text{-}\eta^1\text{:}\eta^1$, with the exception of our η^5 -pyrazolato complex of ruthenium.^[2] Until recently, η^2 coordination of pyrazolato ligands was extremely rare outside of lanthanide and actinide complexes.^[1, 3, 4] Since 1997, we have reported many early transition metal complexes containing η^2 -pyrazolato ligands.^[5, 6] In addition, main group element complexes with η^2 -pyrazolato ligands have been reported in the past several years.^[7–12] A significant open question relates to the occurrence of η^2 -pyrazolato ligands among transition metal complexes with partially filled d shells, where repulsions between the filled d orbitals and pyrazolato nitrogen atoms might destabilize η^2 -pyrazolato coordination in favor of other coordination modes. Mösch-Zanetti has reported the synthesis and structure of tris(3,5-di-*tert*-butylpyrazolato)titanium(III) and several other titanium(III) pyrazolato complexes, and found η^2 coordination of the pyrazolato ligands in these d¹ systems.^[13] However, there have been no reports of η^2 -pyrazolato ligand coordination among the complexes of the Group 4–11 metals with d² or higher electronic configurations. Herein, we report the synthesis and characterization of tris(3,5-di-*tert*-butylpyrazolato)chromium(III) and tris(3,5-di-*tert*-butylpyrazolato)iron(III). These complexes contain η^2 -pyrazolato ligands, and establish that η^2 coordination is possible despite the d³ and d⁵ configurations. We have also carried out molecular orbital calculations on model chromium(III) and iron(III) pyrazolato complexes. While theory predicts that η^2 -pyrazolato ligands are more stable than η^1 -pyrazolato ligands for chromium(III), the opposite trend is found for iron(III). The observation of a stable iron(III) η^2 -pyrazolato complex suggests that the steric bulk of the substituents in the 3- and 5-positions of the pyrazolato ligands plays a pivotal role in stabilizing η^2 -pyrazolato ligands relative to other coordination modes.

Treatment of trichlorotris(tetrahydrofuran)chromium(III) or iron(III) chloride (1 equiv) with potassium 3,5-di-*tert*-butylpyrazolate^[8] (3 equiv) in tetrahydrofuran or diethyl ether led to the formation of tris(3,5-di-*tert*-butylpyrazolato)chromium(III) (**1**, 66%) and tris(3,5-di-*tert*-butylpyrazolato)iron(III) (**2**, 22%) as deep purple and orange-red crystals, respectively, after crystallization from hexane [Eq. (1)]. The



structures of **1** and **2** were established by a combination of spectroscopic and analytical techniques, and by X-ray crystal structure determinations. Both complexes are paramagnetic and show only very broad singlets in the ¹H NMR spectra.

EPR spectra of **1** and **2** were recorded in a toluene glass at 5 K. Both complexes exhibit spectra consistent with high-spin, octahedral metal ions.^[14] The EPR spectra of **1** and **2** are virtually identical to spectra previously reported for high-spin, octahedral tris(2-trimethylsilylamidopyridinato)chromium(III)^[15a] and the analogous axially symmetric iron(III) complex.^[15b] The magnetic moment for **1** was found to be $\mu_{\text{eff}} = 3.43 \mu_{\text{B}}$, which is close to the spin-only magnetic moment expected for three unpaired electrons (3.87 μ_{B}). For **2**, $\mu_{\text{eff}} = 6.10 \mu_{\text{B}}$, which is close to the spin-only magnetic moment expected for five unpaired electrons (5.92 μ_{B}).

Complex **1** exists in the solid state as a monomeric complex with three η^2 -pyrazolato ligands (Figure 1).^[16] The pyrazolato ligands are canted slightly away from perfect trigonal-prismatic geometry toward a three-bladed propeller. The

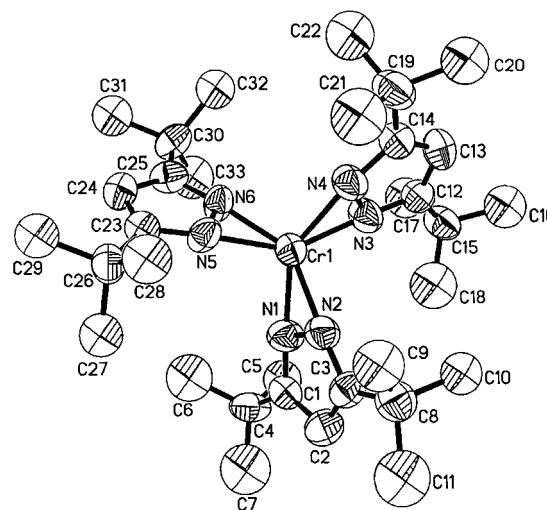
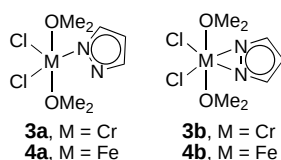


Figure 1. Perspective view of **1**. Selected bond lengths [Å] and angles [°]: Cr1–N1 1.978(3), Cr1–N2 1.981(3), Cr1–N3 1.963(3), Cr1–N4 1.985(3), Cr1–N5 1.983(3), Cr1–N6 1.978(3), N1–N2 1.362(4), N3–N4 1.366(4), N5–N6 1.371(4); N1–Cr1–N2 40.24(11), N3–Cr1–N4 40.50(11), N5–Cr1–N6 40.51(11), N1–Cr1–N3 109.91(13), N1–Cr1–N4 143.05(13), N1–Cr1–N5 100.05(13), N1–Cr1–N6 112.76(12), N2–Cr1–N3 99.62(13), N2–Cr1–N4 111.44(13), N2–Cr1–N5 111.55(13), N2–Cr1–N6 145.15(13), N3–Cr1–N5 147.50(13), N3–Cr1–N6 112.90(13), N4–Cr1–N5 115.17(13), N4–Cr1–N6 101.63(13), Cr1–N1–N2 70.01(19), Cr1–N2–N1 69.75(18), Cr1–N3–N4 70.60(19), Cr1–N4–N3 68.90(18), Cr1–N5–N6 69.53(18), Cr1–N6–N5 69.95(18).

pyrazolato ligands are coordinated to the chromium atom with nearly perfect η^2 geometry, with Cr–N bond lengths ranging from 1.956(6) to 1.986(6) Å. The N–Cr–N angles within each η^2 -pyrazolato ligand are also very similar, and vary from 40.24(11) to 40.51(11)°. The structural parameters of **1** are very similar to those reported for tris(η^2 -3,5-di-*tert*-butylpyrazolato)aluminum,^[9] tris(η^2 -3,5-di-*tert*-butylpyrazolato)scandium,^[11] and tris(η^2 -3,5-di-*tert*-butylpyrazolato)titanium.^[13] The crystal structure of **2**·(C₆H₁₄)_{0.5} was also determined, and the structural parameters are very similar to those of **1**. Crystals of **2**·(C₆H₁₄)_{0.5} were only solved with inclusion of twinning parameters and will be discussed in a later publication.

To gain insight into the preference of η^1 versus η^2 bonding, ab initio calculations were performed on the simplified model



complexes **3** and **4** at the B3LYP/6-311G* level of theory.^[18, 19] The optimized structures of **3b** and **4b** are in good agreement with the X-ray crystal structure data (Cr–N(calcd) = 2.03, 2.02 versus Cr–N(X-ray) = 1.956(6)–1.986(6) Å; Fe–N(calcd) = 2.06, 2.06 versus Fe–N(X-ray) = 2.008(2), 2.009(2) Å).

The charge on the pyrazolato ligand in **3b** was –0.58 and was –0.65 in **4b** (natural population analysis^[20]), making the nitrogen–metal bonding slightly more ionic than in titanium(IV) complexes that we have previously reported.^[5] Similar to our previous molecular orbital studies of titanium(IV) complexes,^[5] η^2 bonding occurred through interaction of molecular orbitals containing symmetric and antisymmetric combination of the nitrogen lone pairs with the empty hybridized 3d and 4s orbitals, as depicted in Figure 2 for **4b**. Consequently, **3b** is 6.6 kcal mol^{–1} more stable than **3a**. In

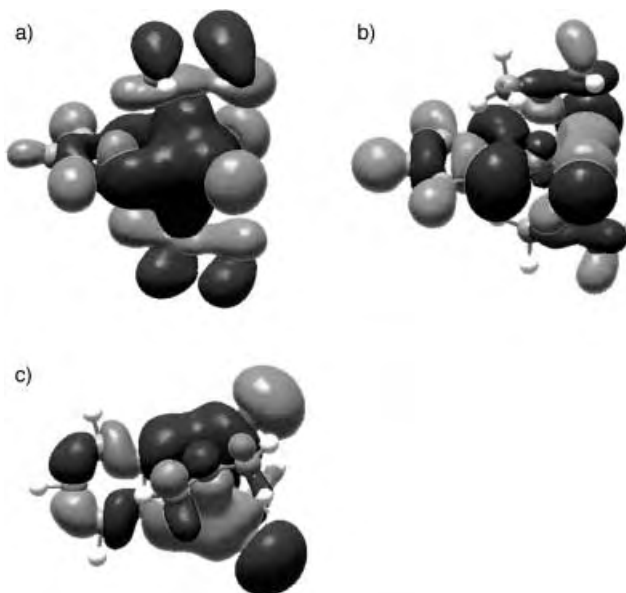


Figure 2. Calculated molecular orbitals showing a) symmetric lone pair of **4b**, b) symmetric lone pair of **4b**, and c) antisymmetric lone pair of **4b**.

high-spin **4**, all five d orbitals formally are singly occupied and are significantly lower in energy than the nitrogen lone pair orbitals, resulting in very little orbital interaction. One of the orbitals containing the symmetric combination of the nitrogen lone pairs forms an antibonding interaction with a d orbital on iron, but the other orbitals have minimal interaction with the iron atom. Due to this change in the orbital interaction, η^2 -pyrazolato bonding in **4** is weakened relative to that in **3**. By contrast, the nitrogen lone pair in the **4a** interacts with the 3d and 4s orbitals on iron, stabilizing **4a** by 1.9 kcal mol^{–1} relative to **4b**.

The crystal structures of **1** and **2** document the first examples of η^2 -pyrazolato ligand coordination in complexes of metal ions with d² or higher electronic configurations. The results of the molecular orbital calculations on **3** and **4** demonstrate that, in the absence of steric effects, η^2 coordi-

nation becomes less stable than η^1 at the d⁵ configuration of iron(III). Consistent with our theoretical model, pyrazolato complexes of the mid to late d-block metals have exhibited either η^1 - or μ - η^1 : η^1 -pyrazolato coordination modes.^[1] As specific relevant examples, bis(pyrazolato)iron(II)^[21, 22] and tris(pyrazolato)iron(III)^[22] are polymeric with μ , η^1 : η^1 -pyrazolato ligands.^[23] Based upon our results, we predict that octahedral homoleptic pyrazolato complexes with d⁵ or higher electronic configurations will not exhibit η^2 -pyrazolato ligands *in the absence of steric effects*. However, the 3,5-di-*tert*-butylpyrazolato ligand and other pyrazolato ligands with bulky substituents may lead to η^2 bonding in metal complexes with high d-electron counts. We note that the 3,5-di-*tert*-butylpyrazolato ligand has seen very little use in the coordination chemistry of the mid to late d-block metals. The present work implies that this ligand and related azolato ligands containing bulky substituents may exhibit much different coordination chemistry than azolato ligands substituted with hydrogen, small hydrocarbon groups, or other moieties with small steric profiles.

Experimental Section

1: A 100-mL Schlenk flask was charged with trichlorotris(tetrahydrofuran)chromium(III) (0.500 g, 1.33 mmol), 3,5-di-*tert*-butylpyrazolotopotassium (1.166 g, 5.34 mmol), and tetrahydrofuran (50 mL). After the mixture had been stirred for 16 h at ambient temperature, the solvent was removed under reduced pressure to yield a purple solid. This solid was extracted with hexane (50 mL) and the resultant solution was filtered through a 2-cm pad of Celite on a coarse glass frit. The deep purple filtrate was placed in a –20 °C freezer for 36 h to afford **1** as deep purple crystals (0.521 g, 66%); m.p. 252 °C (decomp); IR (Nujol): $\tilde{\nu}$ = 1570 (w), 1515 (m), 1361 (s), 1309 (m), 1241 (s), 1207 (w), 1116 (w), 1011 (m), 1003 (m), 790 (s), 714 (m) cm^{–1}; ¹H NMR (C₆D₆, 22 °C): δ = 2.89 (br. s, C(CH₃)₃); elemental analysis (%) calcd for C₃₃H₅₇CrN₆: C 67.20, H 9.74, N 14.25; found: C 67.00, H 9.74, N 14.25.

2: In a fashion similar to the preparation of **1**, iron(III) chloride (0.318 g, 1.96 mmol) was treated with 3,5-di-*tert*-butylpyrazolotopotassium (1.500 g, 6.87 mmol) in diethyl ether (50 mL) to afford **2** as orange-red crystals (0.250 g, 22% yield); m.p. 229 °C (decomp); IR (Nujol): $\tilde{\nu}$ = 1516 (m), 1363 (s), 1291 (w), 1251 (m), 1228 (s), 1204 (m), 1013 (w), 980 (m), 796 (s), 711 (m) cm^{–1}; ¹H NMR (C₆D₆, 22 °C): δ = 6.38 (br. s, C(CH₃)₃); elemental analysis (%) calcd for C₃₃H₅₇FeN₆: C 66.76, H 9.68, N 14.16; found: C 66.70, H 9.54, N 14.26.

Received: December 11, 2001 [Z18362]

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Hexagonal and Cubic Thermally Stable Mesoporous Tin(IV) Phosphates with Acidic and Catalytic Properties**

Christian Serre,* Aline Auroux, Antonella Gervasini, Maryvonne Hervieu, and Gérard Férey

Since the initial work of Mobil researchers on the synthesis of mesoporous silica,^[1] a lot of work has been devoted to extend the composition of mesoporous materials to metal oxides other than silica for applications in acid, redox catalysis, or photocatalytic processes.^[2–4]

[*] Dr. C. Serre, Prof. Dr. G. Férey
Institut Lavoisier, UMR CNRS 8637
Université de Versailles St-Quentin en Yvelines
45 Avenue des Etats-Unis, 78035 Versailles Cedex (France)
Fax: (+33)1-3925-4358
E-mail: serre@chimie.uvsq.fr

Dr. A. Auroux
Institut de Recherches sur la Catalyse, CNRS
2 avenue Einstein, 69626 VILLEURBANNE Cedex (France)

Dr. A. Gervasini
Dipartimento di Chimica Fisica ed Electrochimica
Università degli Studi di Milano
via C. Golgi 19, 20133 Milano (Italy)

Prof. Dr. M. Hervieu
CRISMAT, ISMRA, UMR CNRS 6508
6 Boulevard du Maréchal Juin, 14050 Caen (France)

[**] Dr. F. Taulelle and C. Lorentz (Laboratoire Chimie et RMN du solide, Université Louis Pasteur, Strasbourg, France) and Prof. J. C. Dumas (LAMMI, Université Montpellier II, Montpellier, France) are gratefully acknowledged for their collaboration in NMR and Mössbauer experiments.

To date, a wide range of non-silica based mesostructured solids such, as metal oxides^[5–10] of Al, Ti, Nb, V, W, and Sn or metal phosphates of Al, Zr, or V have been reported.^[11–13] Most of these materials are, however, not stable to the removal of the surfactant and/or lack of long-range order. To our knowledge, cubic mesoporous solids are still scarce in spite of promising results with oxides of Nb,^[14] Sb,^[15] Al-B,^[16] Ti,^[6b] and Zr^[17]. The first mesotextured metallophosphate with a cubic structure was described recently by Mizuno et al.^[18] However, its framework collapses after the removal of the surfactant.

We recently reported new hexagonal or lamella titanium(IV) fluorophosphates synthesized by the fluoride route.^[19] By extending this pathway to the tin(IV) system, we obtained hexagonal and cubic thermally stable porous tin(IV) fluorophosphates. Several mesotextured tin oxides were reported previously,^[10] however, our solids are the first tin-based mesoporous materials exhibiting both a high thermal stability, long-range order, and high surface areas. The cubic phase is also the first thermally stable cubic mesoporous non-silicated metallophosphate reported to date. Finally, the acidic character determination as well as deNO_x catalytic tests (catalysts for the removal of NO_x) are reported.

The existence of either hexagonal or cubic phases is strongly dependent on synthesis parameters, such as concentration, P/Sn, S/Sn ratios (where S = surfactant), and the alkyl chain lengths. Hexagonal solids are obtained for long alkyl-chain surfactants ($n > 14$) while cubic phases appear for short-chain surfactants ($n < 14$). With $n = 14$, either hexagonal or cubic solids are obtained by tuning the P/Sn and/or S/Sn ratios. At a fixed surfactant concentration (S/Sn = 0.5), two phosphoric acid contents, P/Sn = 4 or 16, lead, respectively, to the formation of hexagonal and cubic solids while at a fixed phosphoric acid ratio (P/Sn = 16), hexagonal and cubic solids are obtained, respectively, at S/Sn = 1 and 0.5. At $n = 16$, changing the steric hindrance of the surfactant polar head by using cetyldimethylethylammonium bromide instead of cetyltrimethylammonium bromide (CTAB), leads either to hexagonal or cubic solids depending on the P/Sn ratio.

Both quantitative and thermal analysis reveal that both as-synthesized solids are tin fluorophosphates with P/Sn, F/Sn, and S/Sn (calculated) ratios close to 1.35, 1, and 0.65 (hexagonal) or 1.55, 0.65 and 0.45 (cubic), respectively. These results give approximate compositions of Sn₃(PO₄)₄F₃ · 2TTAB (TTAB = tetradecyl trimethylammoniumbromide) and Sn₂(PO₄)₃F · TTAB, respectively, for the two phases. Both solids are calcined under air at 400 °C, and on cooling to room temperature, the calcined forms rehydrate to some extent without modification of the framework. Quantitative analysis and solid state ¹⁹F, ³¹P, and ¹¹⁹Sn NMR spectra indicate that the resulting solids are rehydrated tin(IV) phosphates that contain only traces of fluorine. Mössbauer experiments indicate also that the two solids possess only octahedrally coordinated tin centers in the +IV oxidation state.

The X-ray patterns (Figure 1) of the as-synthesized TTAB solids ($n = 14$) are characteristic of the hexagonal MCM-41 compound,^[1] and of the cubic micellar mesoporous solid SBA-1,^[15, 20] respectively. Both structures are, on the whole, retained upon calcination. Their thermal stability, up to

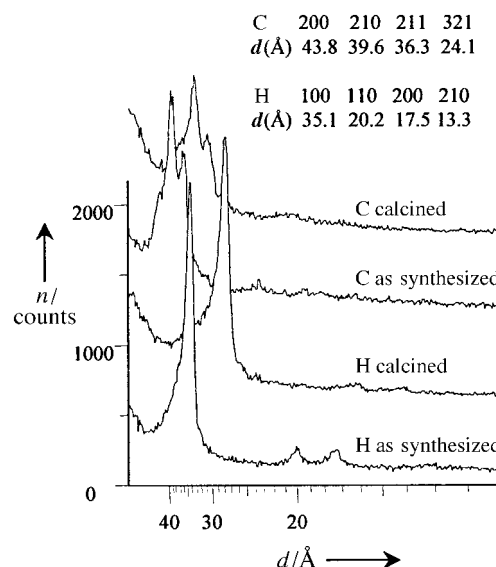


Figure 1. X-Ray powder diffraction patterns of the as-synthesized and calcined forms of the hexagonal (H) and cubic (C) tin(IV) phosphates obtained using TTAB surfactant. A peak index of the as-synthesized solids is given at the top of the Figure.

600 °C, is almost identical. Calcined solids still exhibit a long-range organization since second-order diffraction peaks ((110) and (200) for H and (321) for C) are still visible in the X-ray patterns even if their intensity has slightly decreased. The pore contraction is within the 8–10 Å range in both cases.

Brunauer–Emmet–Teller (BET) experiments, performed on the TTAB hexagonal (H) and cubic (C) solids calcined under air at 400 °C, indicate specific surface areas of 350 (H) and 425 (C) m² g^{−1}, respectively. These values are constant since tin phosphates exhibit a much higher framework density than pure SiO₂. Both N₂ adsorption–desorption isotherms are of type I and do not show hysteresis loops (Figure 2). Schüth and co-workers observed similar isotherms with mesoporous titanium oxophosphates and explained this through the presence of “supermicropores” within the 15–20 Å range.^[6c] Transmission electron microscopy (TEM) experiments (see below) indicate that the pore wall thickness is about 15 Å in both cases; considering the important pore contraction that occurs upon calcination, this gives an estimated pore size for each solid of below 20 Å. This size is consistent with results obtained previously with SBA-1 where

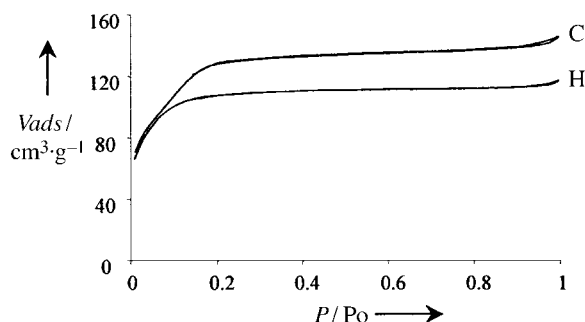


Figure 2. N₂ adsorption–desorption isotherm of the TTAB hexagonal (H) and cubic (C) tin(IV) phosphate solid calcined at 400 °C under air.

the pore size was estimated at about 20 Å for a sample displaying a very narrow hysteresis loop. Finally, by changing the nature of the surfactant (alkyl chain length, polar head), cubic or hexagonal solids, with surface areas between 200 and 630 m² g⁻¹ and pore sizes within the 12–25 Å range, are obtained.

High resolution TEM was performed on two solids: an H sample (CTAB-hexagonal) and a C sample (TTAB-cubic). Images show that the two materials, hexagonal and cubic, are not amorphous but clearly organized. Each of the grains is made of one or several randomly oriented small domains with a periodicity of the order of several nanometers. For the H sample, the electron-microscopy images exhibit a contrast which can be described as an unperfected honeycomb-like arrangement of six-fold faceted spheroids (Figure 3). The average periodicity of the close-packed spheroids is close to 45 Å, which is consistent with the X-ray diffraction results: $a = d(100) \frac{2}{\sqrt{3}} \approx 45.5 \text{ Å}$.

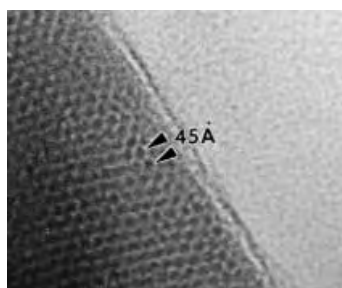


Figure 3. High-resolution electron micrograph showing the organized CTAB hexagonal domains of the as-synthesized tin(IV) phosphate solid.

Concerning the C system, globular cages, such as those observed with SBA-1 are present (Figure 4).^[15] The cages are surrounded by dark rings because of the higher electron density of the tin phosphate framework. Within each organized arrangement of particles, we can distinguish the bright core of the particles, correlated with a zone of low electron density corresponding to the surfactant moieties. Numerous high resolution images were recorded. No preferential orientation of the grains is observed and the images suggest that the symmetry is of a P-type ($h k 0$: no condition, $h 0 l$: $l = 2n$ and $h h l$: $l = 2n$). This symmetry is consistent with a pseudo-cubic (or tetragonal) lattice of a P-type symmetry with a $c \approx 80 \text{ Å}$. This value is smaller than the parameter reported for the as-synthesized SBA-1: $a \approx 89 \text{ Å}$,^[20] but in agreement with

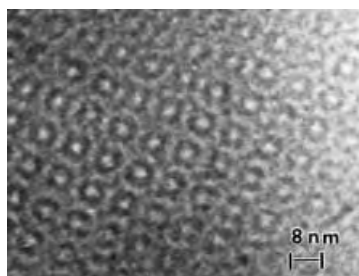


Figure 4. High resolution electron microscopy micrograph of the organized pseudo-cubic domains of the as-synthesized TTAB-cubic tin(IV) phosphate solid.

the use of a smaller alkyl-chain surfactant ($n = 14$) compared with SBA-1 (CTAB ($n = 16$)).

Electron microscopy images also show that, in both cases, no system of sharp reflections is detectable by working in selected-area electron diffraction (SAED) mode. Thus, the pore walls of these solids exhibit no crystallinity unlike the hexagonal titanium fluorophosphates reported.^[19] Energy dispersive spectroscopy (EDS) indicates for both solids (H and C) that the pore walls exhibit a stoichiometry of three tin atoms per four phosphorus centers ($\text{Sn/P} = 0.75$). This result is in relatively good agreement with quantitative analysis results ($\text{Sn/P} \approx 0.73$ and 0.65 , respectively, for phases H and C).

Tin(IV) is well-known for its acidic properties. Therefore, a microcalorimetric study of the NH_3 adsorption was performed on the calcined forms of H and C TTAB solids. The proportion of acidic sites as a function of the binding energy was determined for each solid, which indicated (Figure 5) that

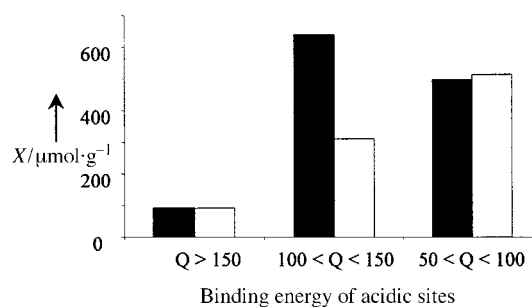


Figure 5. Comparative amount of the acidic sites of the calcined TTAB hexagonal (■) and cubic (□) solids as a function of their binding energy.

both solids are strongly acidic with a large proportion of sites presenting a heat evolved above 100 kJ mol⁻¹. These solids and especially the hexagonal phase, are thus more acidic than MCM-41 and on the whole as acidic as some H-ZSM-5.^[21] The hexagonal form is more acidic than the cubic phase. The number of acidic sites, the strength of which is between 100 and 150 kJ mol⁻¹, is two times higher for the hexagonal phase than for the cubic phase. However, the number of weak sites is similar for the two samples.

Since a deNO_x catalytic activity requires acidic properties and as tin(IV)-containing amorphous oxides are well known for their activity in the reduction of NO by hydrocarbon,^[22, 23] deNO_x catalytic tests were performed on these mesoporous solids.

The two samples were evaluated in the $\text{NO-C}_2\text{H}_4\text{-O}_2$ reaction performed in lean conditions (in excess oxygen). Significant conversion of NO into N_2 as well as of C_2H_4 into CO_2 were detected between 400 and 600 °C. Plotting N_2 yield versus temperature gave a Volano-shaped curve, as usually observed for most deNO_x catalysts.^[23] The maximum amount of N_2 produced was observed around 475 °C for both the samples, hexagonal tin phosphate being more active than the cubic tin phosphate (30 and 20% of N_2 formation, respectively). To indicate the differences between the two samples, Figure 6 shows the profiles of N_2 formation expressed in terms of activity per surface unit obtained for the two samples in the whole temperature range investigated. The better activity of the hexagonal form of tin(IV) phosphate

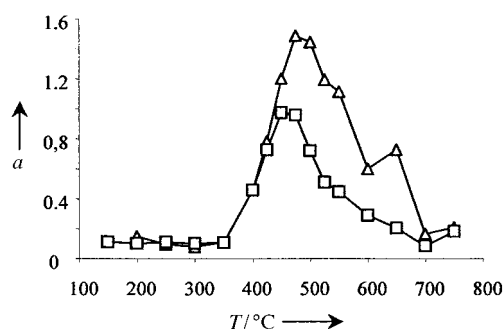


Figure 6. Intrinsic activity a ($10^5 \mu\text{mol N}_2 \text{m}^{-2} \text{min}^{-1}$) of N_2 formation from NO reduction by C_2H_4 in oxygen atmosphere on TTAB hexagonal (Δ) and cubic ($\square$) tin phosphate solids.

could arise from different coordination of the tin(IV) centers and/or a higher amount of tin(IV) species exposed at the surface with respect to the cubic phase.

Besides nitrogen, by-products, such as nitrous oxide and nitrogen dioxide, were present in the reactor outlet at very low concentration, around 10–15 ppmv of NO_2 and 40–50 ppmv for N_2O . This behavior indicates a good selectivity of the samples.

Finally, a synthesis route in aqueous medium leading to thermally stable hexagonal and cubic mesoporous tin(IV) phosphates has been developed. These solids exhibit strong acidic properties and first catalytic tests have shown positive results especially for the hexagonal phase. Comparing their catalytic performances with those of known amorphous catalysts,^[22] it seems that these new compounds could represent an interesting family of materials with good catalytic properties. Other catalytic experiments are currently in progress to evaluate the catalytic behavior of these new mesoporous solids.

Experimental Section

These solids were prepared by mixing SnF_4 with an aqueous solution of phosphoric acid with a final P/Sn ratio between 4 and 16. Then, the surfactant (cetyl or tetradecyl trimethylammoniumbromide (CTAB or TTAB)) solution was added to the stirred first solution (S:Sn ratio: 1:2). The final tin concentration was 0.1 mol L^{-1} . The suspensions were aged at 90°C overnight in a Teflon-lined PARR bomb and cooled to room temperature. The solids, filtered, washed, and dried were calcined under air at $150/400^\circ\text{C}$ for 1 and 8 h, respectively.

X-ray powder diffraction was conducted on a conventional high resolution (θ - 2θ) Siemens D5000 diffractometer using $\lambda_{\text{CuK}\alpha}$. Tin, phosphorus, fluorine, carbon, nitrogen, and hydrogen contents were determined at the C.N.R.S. Central Laboratory of Analysis of Vernaison (69, France). The surface area measurements were measured with a Micromeritics ASAP 2010 apparatus using nitrogen (N_2) as the adsorbed gas. The high resolution electron microscopy (HREM) was performed with a TOPCON 002B microscope (point resolution of $1.8 \text{ \AA}$) equipped with an energy dispersive spectroscopy (EDS) analyzer. Samples were prepared by dispersing the powder in alcohol without grinding.

The microcalorimetric studies of ammonia adsorption were performed at 353 K in a heat-flow calorimeter of the Tian-Calvet type (C80 from Setaram) linked to a conventional volumetric line. Before each experiment the samples were outgassed overnight at 673 K . The differential heats of adsorption were measured as a function of coverage by repeated addition of amounts of gas until an equilibrium pressure of about 66 pa was reached. Then, the samples were evacuated for 1 h at the adsorption temperature and a second adsorption was carried out to allow the determination of chemisorption uptakes.

The catalytic tests were carried out with samples of mass 0.15 g contained in a quartz tubular microreactor (5 mm internal diameter). The reactant stream was provided from a set of mass-flow controllers (Bronkhorst, Hi-Tec) supplying 1000 ppmv NO and $1000 \text{ ppmv C}_2\text{H}_4$, and 20000 ppmv O_2 in helium at a total flow rate of 50 cm^3 (standard temperature and pressure) min^{-1} , with the reactor at close to atmospheric pressure. Contact time was maintained constant at $0.168 \text{ kg s L}^{-1}$. The exit gas stream from the reactor flowed through a gas cell (path length 2.4 m , multiple reflection gas cell) in the beam of an FTIR spectrometer (Bio-Rad with DTGS detector), to give analyses for NO , N_2O , and NO_2 for N-containing species, and C_2H_4 , CO , and CO_2 for C-containing species. The measurements were carried out at 0.50 cm^{-1} resolution with an accuracy of $\pm 10 \text{ ppmv}$ for NO , and 4 for N_2O and NO_2 using lines at 1876 , 2225 , and 1619 , respectively.

The samples were contained in the reactor between plugs of quartz wool and initially pretreated in flowing $20\% \text{ O}_2/\text{He}$ while the temperature was raised in stages up to 350°C and maintained it for 4 h. The tests were repeated three times using fresh portions of catalyst and working in low (200 – 500°C), high (450 – 750°C), and medium (350 – 600°C) zones of reaction temperature, respectively.

Received: November 22, 2001 [Z18260]

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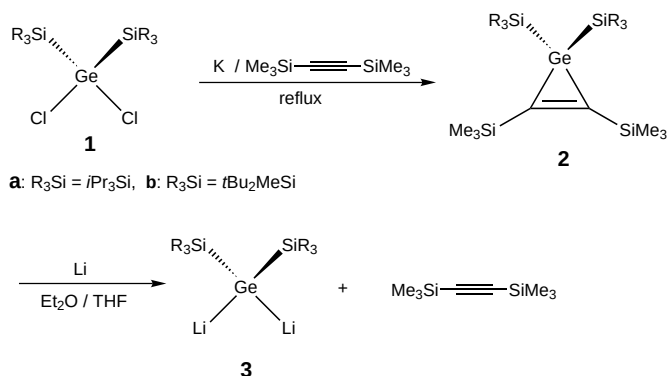
The First Isolable 1,1-Dilithiogermane and Its Unusual Dimeric Structure—An Effective Reagent for the Preparation of Double-Bonded Derivatives of Group 14 Elements**

Akira Sekiguchi,* Rika Izumi, Shinji Ihara, Masaaki Ichinohe, and Vladimir Ya. Lee

Organolithium derivatives are among the most important organometallic compounds in organic chemistry.^[1] The organolithium compounds are well investigated, however, our knowledge of lithium derivatives of heavier Group 14 elements is still very limited. Among the most intensively studied are silyllithium compounds,^[2] whereas very little experimental work on germyllithium derivatives has been published.^[3]

1,1-Dilithiogermane derivatives (R_2GeLi_2) are of interest in view of their synthetic utility, structure, and reactivity. However, there are few reports of dilithiogermane compounds, because of the lack of a useful synthetic method.^[4] In 1999, we reported the unexpected reaction of silacyclopentene with lithium to form a dilithiosilane derivative.^[5] As part of this study, we have examined the reaction of the persilyl-substituted germacyclopentene with lithium and have found the clean formation of $[R_2GeLi_2]$ and bis(trimethylsilyl)acetylene by cleavage of the two Ge–C bonds in the three-membered ring. We herein report the synthesis and isolation of the first stable 1,1-dilithiogermane derivative, its unexpected crystal structure, and its use in the preparation of double-bonded derivatives of heavier Group 14 elements.

As a precursor for 1,1-dilithiogermane, we first prepared germacyclopentenes, from which the generation of the 1,1-dilithiogermane was expected upon reduction with lithium. To date, only six examples of stable germacyclopentenes have been described,^[6] with five of them being structurally characterized. We employed a new method for the preparation of germacyclopentenes, in which the germylene was generated in situ by reduction of the corresponding dichlorogermane **1** with molten potassium, in the presence of bis(trimethylsilyl)acetylene, without solvent (Scheme 1). After 19 h under reflux, the starting chlorogermanes **1a** and **1b** were completely consumed and the corresponding germacyclopentenes, 1,1-bis(triisopropylsilyl)-2,3-bis(trimethylsilyl)-1-germacyclopent-2-ene (**2a**; 83 %) and 1,1-bis(di-*tert*-butyl(methyl)silyl)-2,3-bis(trimethylsilyl)-1-germacyclopent-2-ene (**2b**; 81 %), were formed. The germacyclopentenes **2a** and **2b** were isolated by recrystallization from pentane as air-stable colorless crystals. The crystal structures of both **2a** and **2b**



Scheme 1. Synthesis of germacyclopentenes and dilithiogermanes.

were determined by X-ray analysis and show isosceles-triangle cores with the shortest endocyclic C=C double bond lengths of all germacyclopentenes known to date: 1.317(3) Å for **2a** and 1.317(2) Å for **2b**.^[6,7]

The reduction of both germacyclopentenes **2** with excess lithium in diethyl ether/tetrahydrofuran at room temperature quickly produced a red-brown reaction mixture containing the desired bis(trimethylsilyl)dilithiogermane (**3a**) and bis(di-*tert*-butyl(methyl)silyl)dilithiogermane (**3b**). After the removal of lithium, the solvent, and the bis(trimethylsilyl)acetylene, the oily residue was washed with dry pentane to give 1,1-dilithiogermanes **3a** and **3b** as extremely air- and moisture-sensitive pale yellow powders (Scheme 1). Such 1,1-dilithiogermane derivatives **3** have been isolated as stable compounds for the first time, although the formation of 1,1-dilithiogermanes was proposed some time ago.^[4]

The crystal structure of **3b** was determined by X-ray diffraction analysis (Figure 1).^[7] This structure is rather

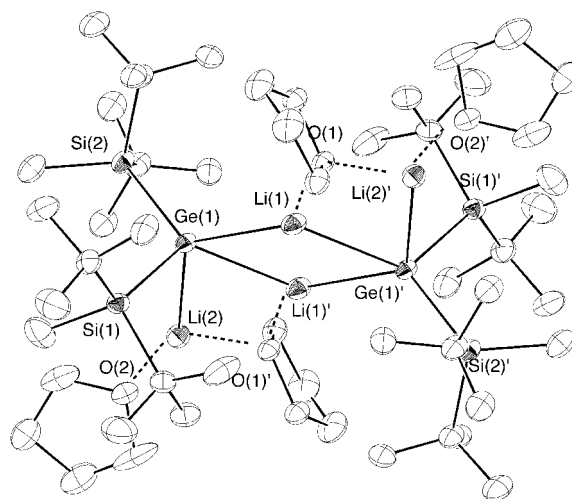


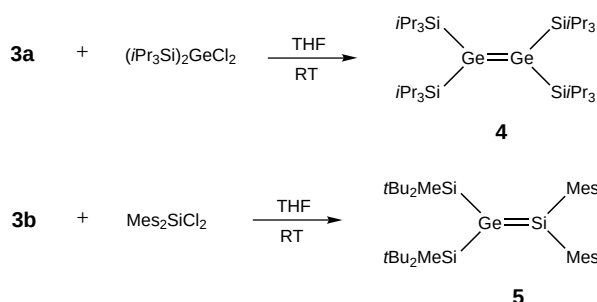
Figure 1. Structure of **3b** (ORTEP plot, thermal ellipsoids set at the 30% level; hydrogen atoms omitted for clarity). Selected interatomic distances [Å] and angles [°]: Ge(1)–Si(1) 2.4026(11), Ge(1)–Si(2) 2.4145(10), Ge(1)–Li(1) 2.664(6), Ge(1)–Li(2) 2.649(6), Li(1)⋯O(1) 2.092(6), Li(2)⋯O(1) 2.041(7), Li(2)⋯O(2) 1.955(6), Li(2)⋯O(1') 2.041(7); Si(1)–Ge(1)–Si(2) 109.42(4), Si(1)–Ge(1)–Li(1) 88.61(14), Si(2)–Ge(1)–Li(1) 101.18(15), Si(1)–Ge(1)–Li(2) 104.94(15), Si(2)–Ge(1)–Li(2) 125.81(14), Li(2)–Ge(1)–Li(1) 120.46(19), Si(1)–Ge(1)–Li(1') 122.52(14), Si(2)–Ge(1)–Li(1') 123.96(14), Li(2)–Ge(1)–Li(1') 63.23(18), Li(1)–Ge(1)–Li(1') 60.8(2), Ge(1)–Li(1)–Ge(1') 119.2(2).

[*] Prof. Dr. A. Sekiguchi, Dipl.-Chem. R. Izumi, Dipl.-Chem. S. Ihara, Dr. M. Ichinohe, Dr. V. Ya. Lee
Department of Chemistry
University of Tsukuba
Tsukuba, Ibaraki 305-8571 (Japan)
Fax: (+81)298-53-4314
E-mail: sekiguch@staff.chem.tsukuba.ac.jp

[**] This work was supported by Grant-in-Aid for Scientific Research (Nos. 12042213, 13440185, 13029015) from the Ministry of Education, Science and Culture of Japan, and TARA (Tsukuba Advanced Research Alliance) Fund.

unusual and shows a dimeric molecule, in which the two lithium atoms Li(1) and Li(1)' are shared by the two Ge atoms, to form an almost regular rhombus Ge(1)-Li(1)-Ge(1')-Li(1)' (Ge(1)-Li(1) = 2.664(6), Ge(1)-Li(1)' = 2.709(6) Å). This arrangement is in sharp contrast to that of the monomeric and symmetrical 1,1-dilithiosilane.^[5] The geometry of the Ge atom in **3b** is far from the ideal tetrahedral: both Ge atoms are pentacoordinated and bound to the three Li atoms (Li(1), Li(1)', and Li(2) for Ge(1); Li(1), Li(1)', and Li(2)' for Ge(1)'). Both Li(1) and Li(1)' atoms have one coordinated THF molecule, whereas each Li(2) and Li(2)' atom is coordinated by two THF molecules. The Si-Ge bond lengths of 2.4026(11) and 2.4145(10) Å, as well as the Ge-Li bond lengths of 2.664(6), 2.649(6), and 2.709(6) Å, lie in the normal range (2.38–2.46 Å for Si-Ge bond lengths,^[8] and 2.61–2.76 Å for Ge-Li bond lengths).^[3d]

As we expected, the 1,1-dilithioorganes **3** are highly reactive. The most important examples of the reactivity of **3** are their coupling reactions with dihalogermane or dihalosilane to form the corresponding digermene or germsilene. Thus, the reaction of **3a** with dichlorobis(triisopropylsilyl)germane cleanly gave the tetrakis(triisopropylsilyl)digermene (**4**).^[9] Reaction of dichlorodimesitylsilane with **3b** allowed us to prepare unsymmetrically substituted 2,2-bis(di-*tert*-butyl(methyl)silyl)-1,1-dimesitylgermasilene (**5**) as a red-brown solid in 77 % yield (Scheme 2).^[10, 11]



Scheme 2. Synthesis of double bonded derivatives of Group 14 elements; Mes = 2,4,6-trimethylphenyl.

Experimental Section

Compound 2b: Dichlorobis(di-*tert*-butyl(methyl)silyl)germane (3.7 g, 8.1 mmol) was heated under reflux with an excess of potassium (2.2 g, 57 mmol) in bis(trimethylsilyl)acetylene (120 mL) for 19 h. After removal of the inorganic salts by filtration and removal of the solvent in vacuo, the residue was recrystallized from pentane to give **2b** as colorless crystals (3.7 g, 81 %). M.p. 125–127 °C (dec.); ¹H NMR (300 MHz, [D₆]benzene, TMS): δ = −0.02 (s, 6H), 0.38 (s, 18H), 1.15 (s, 36H); ¹³C{¹H} NMR (75.5 MHz, [D₆]benzene, TMS): δ = −4.9, 1.2, 22.1, 30.1, 165.3 (C=C); ²⁹Si{¹H} NMR (59.6 MHz, [D₆]benzene, TMS): δ = −9.6, 23.9; HRMS *m/z*: calcd. for C₂₆H₆₀GeSi₄: 558.2989, found: 558.2992.

Compound 3b: The germacyclopentene **2b** (55 mg, 0.1 mmol) was treated with an excess of lithium (15 mg, 2.2 mmol) in a dry, oxygen-free mixture of Et₂O (1.6 mL) and THF (0.4 mL) at room temperature for 2.5 h, to give a red-brown reaction mixture. After the reaction was complete, the solvents and bis(trimethylsilyl)acetylene were removed in vacuo. Then dry toluene (1.5 mL) was added to the solid residue and excess lithium was removed by filtration in a glovebox. After evaporation of toluene, the residue was washed with pentane to give a pale yellow powder **3b** (39 mg, 71 %). ¹H NMR (300 MHz, [D₈]THF, TMS): δ = 0.12 (s, 6H), 1.03 (s, 36H);

¹³C{¹H} NMR (75.5 MHz, [D₈]THF, TMS): δ = −1.4, 21.9, 26.5; ²⁹Si{¹H} NMR (59.6 MHz, [D₈]THF, TMS): δ = 24.0.

Spectral data for **3a**: ¹H NMR (300 MHz, [D₈]THF, TMS): δ = 0.80–1.08 (m, 6H), 1.09 (d, *J* = 7.7 Hz, 36H), ¹³C{¹H} NMR (75.5 MHz, [D₈]THF, TMS): δ = 17.0, 22.1; ²⁹Si{¹H} NMR (59.6 MHz, [D₈]THF, TMS): δ = 31.1.

Received: November 19, 2001 [Z18236]

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Stereoselective Synthesis of Boc-Protected *cis* and *trans*-4-Trifluoromethylprolines by Asymmetric Hydrogenation Reactions**

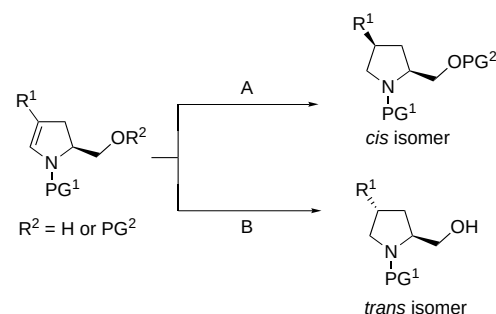
Juan R. Del Valle and Murray Goodman*

The effect of the proline residue on peptide conformation^[1–3] has been the impetus for the design of various unnatural substituted prolines. These amino acid surrogates have featured in a number of biologically active^[4–7] and highly ordered peptides.^[8, 9] Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen-mimetic triple helices, with *trans*-4-fluoroproline yielding the most striking results.^[10–12] The nature of the functional group and the steric constraints imposed by the C4 substituent can greatly influence the conformation of the pyrrolidine ring, as well as the rate of *cis*–*trans* isomerization about the amide bond.^[13–15] For these reasons, the preparation of 4-substituted prolines is an attractive goal in peptidomimetic chemistry.

The synthesis of *cis*-4-phenylproline by a hydrogenolysis reaction, which starts from hydroxyproline was recently described by Hruby and co-workers.^[16] In addition, Nevalainen et al. reported a preparation of Fmoc-*trans*-4-methylproline (Fmoc = 9-fluorenylmethoxycarbonyl) by asymmetric hydrogenation, which yields the desired isomer in a 6:1 diastereomeric ratio before purification.^[17] Although these and other syntheses of 4-substituted prolines are in the literature,^[18–21] a number of desirable targets continue to pose a synthetic challenge. In particular, several *trans*-substituted prolines have been difficult to synthesize with stereo-

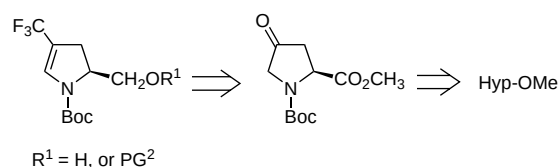
selectivity. In connection with our studies on bioactive and highly ordered peptides, we undertook the synthesis of both stereoisomers of 4-trifluoromethyl-L-proline. These building blocks are expected to have profound conformational effects on their host structures, which arise from the electronegative nature of the trifluoromethyl group.

Our strategy for the preparation of the title compounds employs asymmetric hydrogenation of the pyrrolines shown in Scheme 1. For the synthesis of the *cis* isomer, the facial



Scheme 1. Strategies for the asymmetric hydrogenation of pyrroline intermediates. A = Sterically directed hydrogenation, B = hydroxy-directed hydrogenation.

selectivity of the hydrogenation was expected to depend on steric factors, which result from protection of the hydroxy functionality as an ether or ester moiety. We were unable to find previous syntheses of *trans*-substituted prolines that exploit the potential for hydroxy-directed hydrogenation of pyrroline intermediates. We envisioned this as a viable route towards the *trans*-proline isomer as well as related analogues. The retrosynthesis in Scheme 2 shows Boc-4-prolinone (Boc = *tert*-butoxycarbonyl) as a precursor to the desired pyrrolines.



Scheme 2. Retrosynthesis of Boc-4-trifluoromethyl-L-proline; Hyp = hydroxyproline.

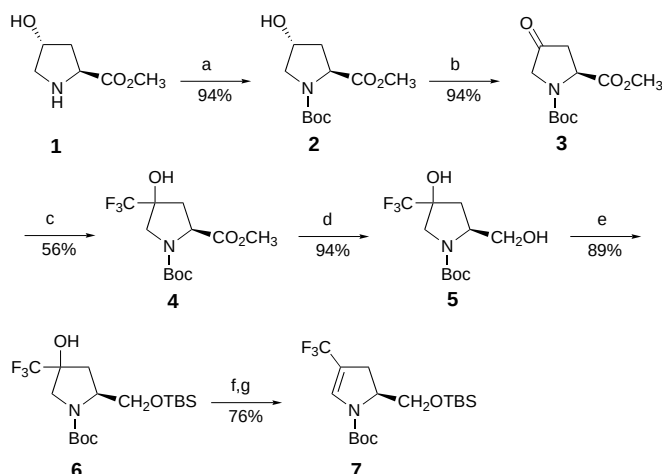
The synthesis of Boc-4-trifluoromethyl-L-proline (Scheme 3) begins with the methyl ester of commercially available and inexpensive *trans*-4-hydroxyproline (**1**). Boc-protection was carried out under normal conditions, followed by oxidation using trichloroisocyanuric acid and catalytic 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical; TEMPO)^[22] to give ketone **3**.

With the protected prolinone in hand, the trifluoromethyl group was introduced by treatment of **3** with trimethyl(trifluoromethyl)silane, in the presence of a fluoride initiator^[23, 24] to afford the tertiary alcohol **4** in 56 % yield. Compound **4** was a single diastereomer which we presumed to be the 2*S*,4*S* isomer from the steric implications of the reaction.

[*] Prof. Dr. M. Goodman, J. R. Del Valle
Department of Chemistry and Biochemistry
University of California, San Diego
La Jolla, CA 92093 (USA)
Fax: (+1) 858-534-0202
E-mail: mgoodman@ucsd.edu

[**] The authors wish to thank Dr. Peter Gantzel for X-ray diffraction studies. This work was supported by a grant from the NSF (DMR-0111617). J.R.D. gratefully acknowledges the support of a San Diego Fellowship; Boc = *tert*-butoxycarbonyl.

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



Scheme 3. Reagents and conditions: a) Boc_2O , triethylamine (TEA), CH_2Cl_2 , 18 h; b) Trichloroisocyanuric acid, TEMPO (cat.), CH_2Cl_2 , 20 min, 0°C ; c) 2 equiv CF_3TMS (TMS = trimethylsilyl), 2.1 equiv TBAF (tetrabutylammonium fluoride), $0^\circ\text{C} \rightarrow \text{RT}$, 24 h; d) NaBH_4 , LiCl, $\text{EtOH}:\text{THF}$ (2:1), RT, 18 h; e) TBDMSCl, TEA, 4-dimethylaminopyridine (DMAP), CH_2Cl_2 , RT, 18 h; f) TosCl (Tos = tosyl), NaH, THF, $0^\circ\text{C} \rightarrow \text{RT}$, 2 h; g) 2 equiv *t*BuOK, THF, -40°C , 2 h.

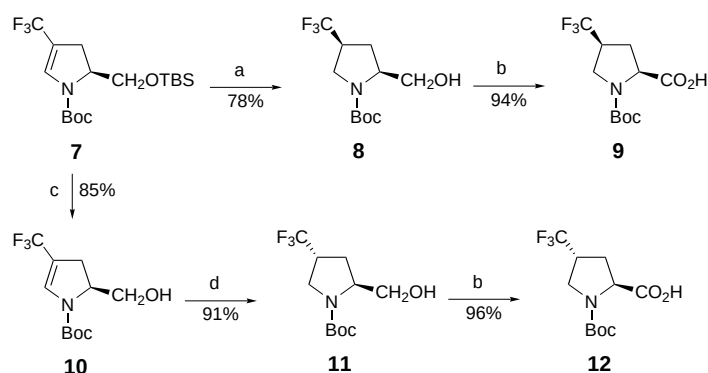
The dehydration of **4** posed a challenge as few reports deal with the effects of trifluoromethyl groups on this transformation. In our initial efforts, reaction of **4** with SOCl_2 /pyridine, *para*-toluenesulfonic acid/benzene, and POCl_3 /DBU yielded none of the desired product. A study on the dehydration of tertiary α -trifluoromethyl alcohols carried out by Nagai and co-workers^[25] found that base-promoted elimination of the corresponding tosylates gave the desired olefins in satisfactory yield. Therefore, **4** was treated with lithium borohydride and the resulting primary alcohol was selectively protected as the *tert*-butyl trimethylsilyl (TBDMS) ether to give **6**. Tosylation of the tertiary alkoxide of **6** proceeded normally and treatment of the product with potassium *tert*-butoxide furnished the key pyrroline intermediate **7** in good yield. Analysis of the crude product mixture revealed a small amount (8%) of the 3,4-olefin that was removed during purification.

Heterogenous hydrogenation of **7** was carried out under a variety of conditions (Table 1). Curiously, hydrogenations with Pd/C resulted in nearly complete removal of the TBDMS protecting group. Despite this, good facial selectivities were observed with the sterically directed *cis* 2*S*,4*S* isomer **8** as the major product in each case. The best selectivity, a 15:1 *cis:trans* ratio, was obtained by using 5% Pd/C in ethyl acetate. The minor diastereomer can be removed by column chromatography to give the *cis* product **8** in 78% isolated yield and >98% diastereomeric excess (Scheme 4).

Table 1. Hydrogenations of pyrroline **7**.

Catalyst	Solvent	<i>cis:trans</i> ^[a]	Yield ^[b]
10% Pd/C	THF	90:10	86%
5% Pd/C	EtOH	92:8	81%
5% Pd/C	EtOAc	94:6	85%
Rh/C	EtOAc	78:22	UD

[a] Determined by ^{19}F NMR analysis of crude mixtures. [b] Crude combined yield (**8** + **11**). UD = undetermined.



Scheme 4. Reagents and conditions: a) H_2 (1 atm), Pd/C, EtOAc, RT, 8 h, 99:1 d.r. after flash chromatography (See Table 1); b) NaClO, NaClO₂, TEMPO, MeCN:pH 6.7 NaH_2PO_4 buffer (0.67 M), 45°C , 24 h; c) TBAF, THF, RT, 30 min; d) H_2 (1 atm), 2 mol % $[\text{Ir}(\text{cod})(\text{py})\text{PCy}_3]$, CH_2Cl_2 , RT, 4 h, 158:1 d.r. (see Table 2).

Oxidation of **8** was carried out using a slight modification to the method described by Zhao et al.^[26] The Boc-amino acid **9** was sufficiently pure after work up for use in peptide synthesis. The absolute stereochemistry of Boc-(4*S*)-trifluoromethyl-L-proline (**9**) was confirmed by X-ray diffraction (Figure 1).

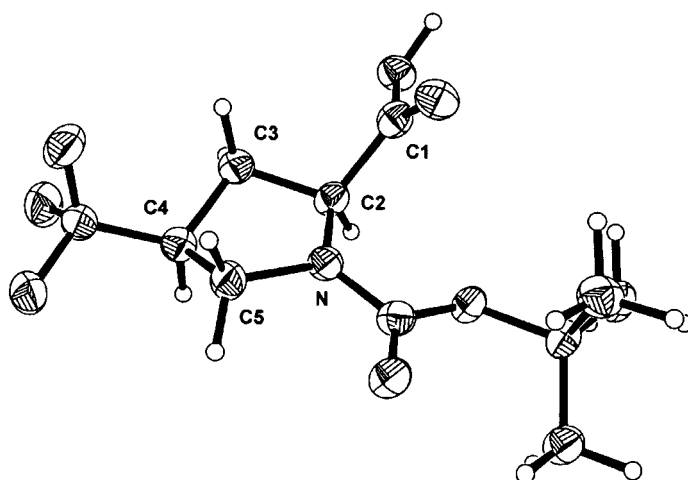


Figure 1. Crystal Structure of **9**.

To prepare the pyrroline intermediate for hydroxy-directed asymmetric hydrogenation, **7** was deprotected to unmask the primary alcohol. The results of the hydrogenations of **10** are summarized in Table 2.

Prior to attempting homogenous reduction, some heterogeneous catalysts were tested. Because the previous hydro-

Table 2. Hydrogenation of pyrroline **10**.

Catalyst	Solvent	<i>cis:trans</i> ^[a]	Yield ^[b]
Raney-Ni	MeOH	70:30	98%
5% Pd/C	PhH	52:48	92%
5% Pd/C	EtOAc	55:45	95%
$[\text{Ir}(\text{cod})(\text{py})\text{PCy}_3]^{\text{[c]}}$	CH_2Cl_2	5:95	96%
$[\text{Ir}(\text{cod})(\text{py})\text{PCy}_3]^{\text{[d]}}$	CH_2Cl_2	1:158	95%

[a] Determined by ^{19}F NMR analysis of crude mixtures. [b] Crude combined yield (**8** + **11**). [c] 15 mol % catalyst. [d] 2 mol % catalyst.

generations with Pd/C heavily favored the *cis* product despite loss of the TBDMS group, we did not expect a significant coordination of the hydroxy group to the palladium catalyst. Nevertheless, reduction of **10** with 5 % Pd/C gave appreciable amounts of the *trans* isomer. After careful chromatographic separation the 1:1 diastereomeric ratio rendered these conditions suitable for preparing both isomers simultaneously. In attempting homogenous hydrogenation, however, we found a divergent approach to be equally practical for the preparation of these building blocks.

Among the numerous catalysts available for homogenous hydrogenation,^[27, 28] the Ir^I compound introduced by Crabtree et al.^[29] has consistently shown excellent selectivity in the hydroxy-directed reduction of cyclic olefins.^[30–32] By employing the Ir^I complex, we observed a dramatic increase in the *trans* selectivity.^[33] Under optimal conditions, treatment of **10** with 2 mol % of [Ir(cod)(py)PCy₃] (cod = cyclooctadiene, py = pyridine) under H₂ resulted in complete conversion into the desired product. The *trans*:*cis* ratio was 158:1, measured by ¹⁹F NMR spectroscopy. Subsequent removal of the catalyst by filtration through a plug of silica gel provided Boc-(4*R*)-trifluoromethyl-L-prolinol (**11**) in a diastereomerically pure form.

Prolinol **11** was oxidized as described above in 96 % yield. The ¹⁹F NMR spectrum of **12** contained two doublet signals in a 1.5:1 ratio. Incremental increases in temperature resulted in the gradual coalescence of the NMR peaks of **12**, confirming the rotamer effect and ruling out epimerization during the oxidation. Thus, the *trans* isomer, Boc-(4*R*,2*S*)-trifluoromethylproline, was synthesized in good overall yield and with complete diastereoselectivity, from hydroxyproline.

In summary, we have described the preparation of both *cis* and *trans*-4-trifluoromethyl-L-proline employing stereoselective substrate-directed hydrogenation reactions. Most noteworthy is the outstanding facial selectivity achieved in the reduction of **10** with the Crabtree catalyst (158:1 d.r.). These results will be applied in the synthesis of various substituted prolines for incorporation into peptides and peptidomimetics.

Received: January 11, 2002 [Z18513]

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In Situ Enzymatic Screening (ISES): A Tool for Catalyst Discovery and Reaction Development**

David B. Berkowitz,* Mohua Bose, and Sungjo Choi

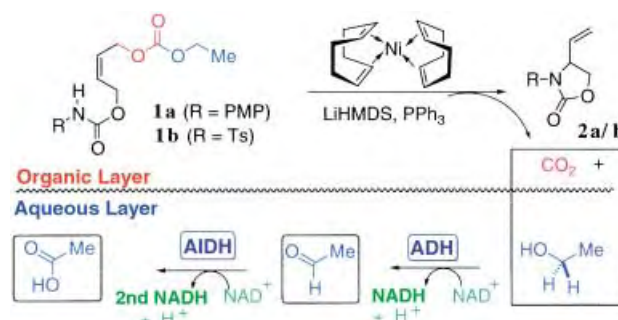
*Dedicated to Professor Samuel J. Danishefsky
on the occasion of his 65th birthday*

The move from the more deliberate, traditional approach to catalyst discovery to combinatorial approaches, has spurred great interest in the development of parallel-screening methods. As Crabtree and Loch recently put it, ideally one seeks “an appropriate chemical sensor in a rapid parallel assay to detect rate and perhaps selectivity”.^[1] Herein, we describe the use of enzymes to report rapidly on reaction rate, for a set of parallel reactions. Seto and Abato recently described the use of enzymes to report on (enantio)selectivity.^[2] From a broader perspective, these developments may be regarded as adding to the versatility of enzymes as tools for the organic chemist, an area that has seen remarkable expansion from asymmetric processing of unnatural substrates^[3–5] and protecting-group cleavage under mild conditions,^[6] to the creation of artificial enzymatic pathways.^[7, 8]

There is currently great interest in “combinatorial catalysis”,^[9] especially in transition-metal (TM) catalyzed reactions, for which reaction discovery and optimization often involve varying 1) the metal, 2) the ligand (type, structure, and stoichiometry), and 3) the substrate structure. By choosing such a model reaction, we sought both to establish proof of principle and to assess the ability of the screen to evaluate such variables one at a time.

In our approach, the organic reaction under study is coupled, *in situ*, with an enzymatic reaction that permits continuous UV spectroscopic monitoring of the reaction. We term this approach ‘*in situ* enzymatic screening’ (ISES). This method is complementary to the previously communicated screening techniques,^[10–19] in that it provides 1) evidence of product formation (not directly available using the elegant IR-thermography method of the Morken and Reetz groups)^[11] and 2) relative rate profiles (not easily available with time-point detection systems employing gas^[12] or liquid chromatography^[10, 13] or mass spectrometry),^[14] 3) without the need to alter the substrate, by installing a chromophore,^[15] a fluorophore,^[16] or an azo-dye precursor.^[17]

Consonant with our interest in developing synthetic methodology toward densely functionalized β,γ -unsaturated amino acids^[20] as inhibitors of PLP-dependent (PLP = pyridoxal phosphate) enzymes,^[21] we chose a TM-mediated allylic-amination reaction as our model reaction. We were influenced, in this regard, by an important precedent from Trost et al.;^[22a] scalemic vinylglycinol had been synthesized through Pd⁰-mediated allylic amination.^[22] We set out to use ISES to identify other TMs, including less expensive ones, which were capable of catalyzing the intramolecular allylic-amination reaction illustrated in Scheme 1.^[23] Success here would, in principle, validate the use of ISES in screening other variants of the allylic-displacement reaction.^[24]



Scheme 1. ISES of catalysts for allylic displacement. PMP = *para*-methoxyphenyl.

A UV spectrophotometer fitted with an automated cell changer was chosen for parallel screening, as this equipment is readily available commercially. Six non-palladium TM catalysts were simultaneously monitored for intramolecular allylic amination with model substrates **1a** and **1b**. Because the TM complexes themselves are highly colored, these reactions are run in a biphasic fashion. The organic chemistry takes place in an upper organic layer, above the spectrophotometer beam, and the linked enzymatic chemistry takes place in a lower aqueous layer, in the path of the beam (Scheme 1). Turnover of the ethyl carbonate substrate in the organic layer leads to release of ethanol, which diffuses into the aqueous layer, where it undergoes enzymatic oxidation with concomitant formation of nicotinamide adenine dinucleotide, reduced form (NADH; $\lambda_{\text{max}} = 340 \text{ nm}$). A coupled alcohol-dehydrogenase (ADH)/aldehyde-dehydrogenase (AIDH) enzyme assay was found to be optimal for screening (Figure 1).^[25]

An appropriate organic solvent for a biphasic ISES screen such as this must: 1) be essentially immiscible in the aqueous buffer, 2) solubilize all the organic substrates and catalysts (here TM complexes) chosen, 3) be compatible with the reaction under study, 4) permit the diffusion of the (by-)product (enzymatic substrate) into the aqueous-buffer layer. Several organic solvents were examined here, and a mixed organic solvent (THF:toluene:hexane 2:1:1) was chosen to fulfil these criteria best (see Supporting Information).^[26, 27]

With this system, one can easily screen six reactions simultaneously, and obtain meaningful relative kinetic data within ten minutes (Figure 2 and Table 1). All screening methods that rely upon the monitoring of a leaving group are susceptible to the false positive that would be observed on

[*] Prof. D. B. Berkowitz, M. Bose, S. Choi
Department of Chemistry
University of Nebraska
Lincoln, NE 68588-0304 (USA)
Fax: (+1) 402-472-9402
E-mail: dbb@unlserve.unl.edu

[**] We thank D. Seebach and S. G. DiMaggio for valuable comments and the referees for suggesting a number of useful control experiments. Financial support from the National Institutes of Health (CA 62034) is gratefully acknowledged. D.B.B. is an Alfred P. Sloan Fellow. This research was facilitated by grants for NMR and GC–MS instrumentation from the NIH and the NSF, respectively.

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

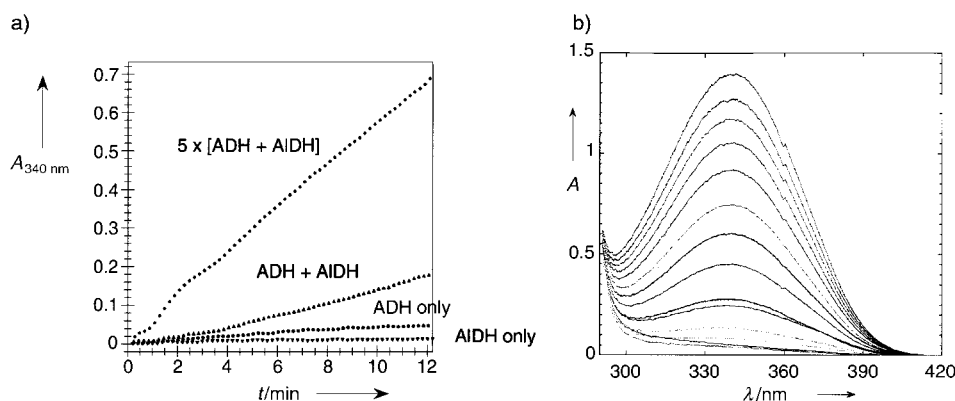
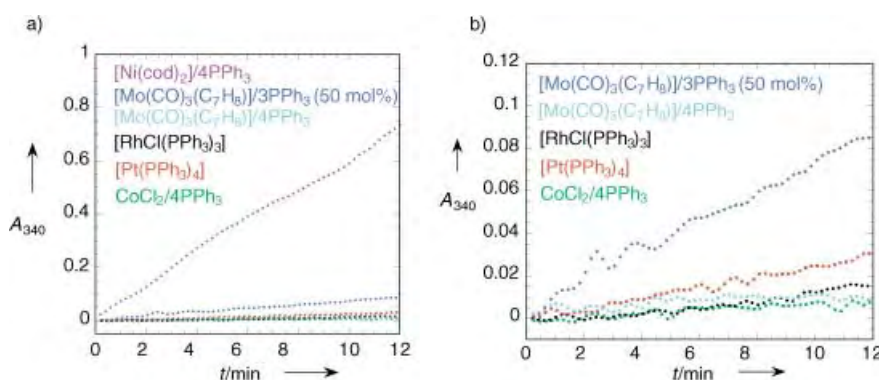


Figure 1. UV spectra showing a) the dependence of NADH formation rate observed upon enzymatic couple used, and right) a clear spectroscopic signature, which indicates that NADH is the species giving rise to the observed 340 nm absorbance increase. All traces are for the reaction in Scheme 1. Spectral scans shown (b) are at two min intervals. The AIDH-only experiment (a) is a negative control and shows no rate, as expected.



Catalyst	Slope [mAbs/min] [a]	Isolated Yield [%]
$[\text{Ni}(\text{cod})_2]/4\text{PPh}_3$	58 [b]	70
$[\text{Ni}(\text{cod})_2]/4\text{PPh}_3$ [c]		(89)
$[\text{Mo}(\text{CO})_3(\text{C}_7\text{H}_5)]/3\text{PPh}_3$ [d]	6.8	18
$[\text{Mo}(\text{CO})_3(\text{C}_7\text{H}_5)]$ [e]		(35)
$[\text{Mo}(\text{CO})_3(\text{C}_7\text{H}_5)]/4\text{PPh}_3$	0.6	[f]
$[\text{Pt}(\text{PPh}_3)_4]$	2.5	15 [g]
$[\text{RhCl}(\text{PPh}_3)_3]$	1.5	= 5 [f]
$\text{CoCl}_2/4\text{PPh}_3$	0.7	[e]

Figure 2. a) UV spectra showing the relative rates of turnover of substrate **1**, inferred from enzymatically coupled EtOH oxidation; b) expansion of (a). For each metal, the Table provides a comparison between the NADH-formation rate observed in the cuvette screen^[30] and the isolated yield of **2** for the same reaction in a round-bottomed (RB) flask.^[31] [a] Slopes of linear least-squares fit lines to the UV spectra shown above. Note: The entries in () represent RB-flask results only, run at higher catalyst loadings; [b] three runs gave values of 55, 58, and 60 mAbs/min, which are consistent with an experimental uncertainty of ± 5 –15% for these ISES slopes; [c] reaction run at 20 mol% catalyst; [d] in both the cuvette and the RB flask, this reaction was run on **1b** at 138 mM substrate (half the usual concentration) and at 50 mol% catalyst; [e] reaction run on **1b** at 100 mol% catalyst at the usual concentration (275 mM); [f] little to no product detected by crude ^1H NMR spectroscopy; [g] for the Pt^0 catalyzed reaction, the rate observed by ISES increases somewhat beyond the initial 12 mins.

hydrolysis of the substrate. This concern necessitates the independent testing “in the reaction flask” of apparent positive results in the cuvette. Only after a significant body of data of this kind is accumulated will it be possible to establish the extent of this potential limitation. In the case at hand, there is a good correlation between relative NADH-formation rates observed and relative product-formation rates in the upper organic layer, as examined independently by an NMR spectroscopic time-point assay.^[28] There is also a

correlation, though less direct, as expected, between relative rates observed in the cuvette and yields obtained for the same reactions in neat THF with one h reaction times (Figure 2).

Across a spectrum of non-palladium TM complexes screened, the most favorable results were obtained with Ni^0 catalysts.^[29] To our knowledge, only a couple of Ni^0 -catalyzed allylic aminations have been reported, and these employ simple secondary amines as nucleophiles. These methods require either stoichiometric amounts of nickel,^[23f] or elevated temperatures.^[23d, e] The cyclization uncovered here, in which a lithiated carbamate serves as intramolecular nucleophile,^[32] is the first example of a room-temperature allylic amination, catalyzed by Ni^0 . The screen also uncovered the first Mo^0 -mediated allylic amination, of which we are aware, albeit in modest yield.^[33]

With Ni^0 centers showing promise, we employed ISES to probe the ligand and nitrogen-PG (PG = protecting group) dependence of this reaction. The results are collected in Table 1 and correspond to data assimilated from three sets of six-cuvette runs. Electron-rich N-protecting groups are beneficial, with the PMP group giving the best rates. This PG was retained for the ligand screens, which turned up three hits (1,4-butanediylbis[(diphenyl)phosphane] (dppb), PPh_3 , dppf); these ligands include the only two bidentate phosphane ligands examined.

Several other control experiments were run to define more precisely the optimal conditions and/or limitations of this biphasic ISES screen. In one, by varying the amount of one dehydrogenase enzyme with the other held constant,^[35] we were able to establish that, under the standard screening conditions chosen here,

the ADH-mediated oxidation of ethanol to acetaldehyde is not at all rate-limiting. On the other hand, the AIDH-mediated oxidation of acetaldehyde to acetic acid is partially rate-limiting. So while, in general, relative rates are reproducible at ± 5 –15% under our standard conditions (Figure 2; this reproducibility points to consistency in AIDH-pipetting), this experimental uncertainty might be reduced even further by expending more AIDH (0.12 $\rightarrow$ 0.24 U) per cuvette, to make neither enzymatic step even partially rate limiting).

Table 1. Nitrogen-protecting-group/ligand screens.

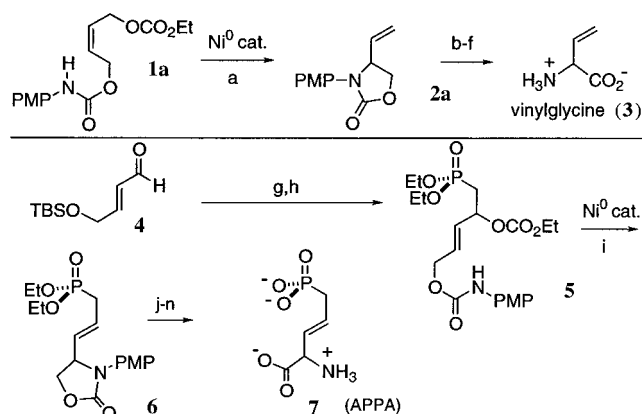
Entry	Ligand (L)	N-Protecting Group (R)	Slope ^[a] [mAbs/min]
1	PPh ₃	H (no protection)	7
2	PPh ₃	CHPh ₂ (benzhydryl)	9
3	PPh ₃	C₆H₂-3,4,5-(OMe)₃ 18	
4	PPh ₃	C ₆ H ₄ - <i>p</i> -NO ₂ (PNP)	0.2
5	PPh ₃	CO ₂ <i>t</i> Bu (Boc)	1
6	PPh₃	C₆H₄-<i>p</i>-OMe (PMP) 35	
7	P(OMe) ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	1
8	P(2,6-di-OMe-C ₆ H ₃) ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	7
9	AsPh ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	0.3
10	2,2'-CH ₂ -(4S)-Ph-box ^[b]	C ₆ H ₄ - <i>p</i> -OMe (PMP)	0.6
11	dppf^[c]	C ₆ H ₄ - <i>p</i> -OMe (PMP)	26
12	P(C ₆ H ₄ - <i>p</i> -NMe ₂) ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	1
13	P(C ₆ F ₅) ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	0.3
14	Ph₂P(CH₂)₄PPh₂	C ₆ H ₄ - <i>p</i> -OMe (PMP)	118
15	P(2-fur) ₃ ^[d]	C ₆ H ₄ - <i>p</i> -OMe (PMP)	0.4
16	P(<i>t</i> Bu) ₃	C ₆ H ₄ - <i>p</i> -OMe (PMP)	0.4

[a] Slopes of least-squares fitted lines to the Abs (absorbance) versus time data over about 10 min.^[34] [b] Box = 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline]. [c] Dppf = 1,1'-bis(diphenylphosphino)ferrocene. [d] fur = furyl.

Perhaps the central issue that arises when one considers the ISES concept is the compatibility of enzymatic chemistry and TM-mediated organic chemistry in a single vessel. While the biphasic nature of this assay is expected to offer a considerable degree of compartmentalization for any screened reaction, it will be important to establish whether components of the aqueous phase (i.e. water and acetaldehyde) diffuse into and inhibit the chemistry in the organic layer. Conversely, one must consider the possibility that components of the organic layer (e.g. metal complexes) inhibit the enzymatic reporter groups in the aqueous layer.

A Karl Fischer titration established that up to 1 weight % diffuses into the organic layer under the screening conditions.^[35] It is noteworthy that not only is the reaction apparently compatible with stoichiometric amounts of water, but, indeed, a considerable variety of organic transformations display aqueous compatibility (see the Supporting Information for references to such reactions). Two experiments were carried out to assess the affect of enzymatically generated acetaldehyde on the TM-mediated reaction in the organic phase. Neither introduction of acetaldehyde into the aqueous layer, nor into the organic layer directly (at 45 mol % levels) produced a decrease in the ISES-monitored reaction rate.^[35] As for the converse direction, control experiments revealed no inhibition of ethanol oxidation in the aqueous layer when standard levels of phosphane ligand and either [Ni(cod)₂] or [(C₇H₈)Mo(CO)₃] were introduced into the organic layer.^[35] These results are consistent with the appearance of a characteristic, unperturbed NADH spectrum in the aqueous layer with time, as the metal-complex-mediated chemistry takes place in the upper organic layer (Figure 1), which suggests that indeed little to no diffusion of these organo-metallic complexes into the aqueous layer is occurring.

Having identified good conditions for this Ni⁰-mediated allylic amination at room temperature, these conditions were applied to the syntheses of two important β,γ -unsaturated amino acids. Vinylglycine (**3**), a known inactivator of PLP-dependent transaminases for L-aspartate, L-alanine, L-serine, and D-alanine^[36] is easily constructed (Scheme 2). It is noteworthy that the key intramolecular allylic-amination step proceeds in excellent yield and that the PPh₃-ligated Ni⁰ catalyst may be generated either by ligand exchange from [Ni(cod)₂] or by Zn-mediated reduction of the corresponding dichloro-Ni^{II} complex.



Scheme 2. a) [Ni(cod)₂], PPh₃, LiHMDS (89%) or Zn⁰, [NiCl₂(PPh₃)₂], LiHMDS (84%); b) CAN, MeCN:H₂O 2:1 (78%); c) Boc₂O, NEt₃, CH₂Cl₂ (88%); d) Cs₂CO₃, MeOH (88%); e) CrO₃, H₂SO₄(aq), acetone (82%); f) TFA, CH₂Cl₂ (84%, isolated as the TFA salt); g) MeP(O)(OEt)₂, *n*-BuLi, THF, -40 °C, 30 min; EtO₂CCl, 30 min; then 0.3 N HCl, warm to RT (68%); h) *p*-MeO-C₆H₄NCO, pyr, (96%); i) 20 mol % [Ni(cod)₂], dppb, LiHMDS (79%); or 20 mol % [Ni(cod)₂], PPh₃, LiHMDS (77%); Zn⁰, or 20 mol % [NiCl₂(PPh₃)₂], LiHMDS (70%); j) CAN, MeCN:H₂O 2:1 (89%); k) Boc₂O, LiHMDS, THF (85%); l) Cs₂CO₃, EtOH (95%); m) CrO₃, H₂SO₄(aq), acetone (76%); n) TMSI, CH₂Cl₂ (80%, isolated as the ammonium salt). CAN = ceric ammonium nitrate, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, pyr = pyridine, TMS = trimethylsilyl, cod = cyclooctadiene, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TBS = *tert*-butyldimethylsilyl.

The same strategy led to an expeditious synthesis of *E*-2-amino-5-phosphono-3-pentenoic acid (**7**; APPA).^[37] This β,γ -unsaturated phosphonate mimic of homoserine phosphate has been shown recently to inhibit two PLP-dependent enzymes: cystathionine γ -synthase (tight-binding reversible inhibitor; $K_i = 27 \mu\text{M}$)^[38a] and threonine synthase (irreversible inhibitor; $K_i = 400 \mu\text{M}$; $k_{\text{inact}} = 0.25 \text{ min}^{-1}$).^[38b] The requisite α -phosphonomethyl allylic carbonate **5** could be assembled easily from aldehyde **4** (Scheme 2). Three operations were carried out in one pot; aldehyde **4** was condensed with diethyl lithiomethylphosphonate at low temperature, followed sequentially by alkoxide trapping with ethyl chloroformate, and in situ desilylation. Pleasingly, with either dppb or triphenylphosphane (tpp) as ligand, the key Ni⁰-mediated allylic amination proceeded both efficiently and stereoselectively, and yielded solely the *E* isomer of **6**.

The ISES approach to catalyst screening demonstrated herein is expected to be applicable to a range of synthetically useful transformations, which includes others that involve release of carbonates or alcohols, and their detection with the

enzyme couple detailed herein, and still others that involve monitoring entirely different products or leaving groups with other enzyme couples.

Received: May 11, 2001

Revised: February 21, 2002 [Z17085]

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- [25] The second enzymatic reaction not only forms a second molecule of NADH for each EtOH equivalent oxidized, but it also converts an unfavorable equilibrium into a highly favorable one. Thus, even at pH 7.7, $\Delta G' = +4.6$ kcal mol⁻¹ for the (ADH-mediated) oxidation of ethanol with NAD⁺, whereas $\Delta G' = -15.2$ kcal mol⁻¹ for the subsequent (AIDH-mediated) oxidation of acetaldehyde to acetate (for a discussion of the equilibrium constants for these oxidations, see: R. A. Alberty, *Arch. Biochem. Biophys.* **1993**, 307, 8–14. The $\Delta G'$ values given here assume an ionic strength of 0.1 and have been corrected for the fixed assay pH). Note: the thermodynamics of the ADH-step can be improved by substitution of APAD⁺ (a better oxidant, but more expensive cofactor; redox potential = -258 mV, λ_{max} = 365 nm) for NAD⁺ (redox potential = -320 mV; λ_{max} = 340 nm). For experimental details of this alternative single-dehydrogenase ISES assay, see the Supporting Information under the heading “Effect of Acetaldehyde on TM-Catalyzed Allylic-Amination Rate”.
- [26] A referee pointed out that, with ISES, one might encounter a “leveling effect”, in which turnover rates that exceed the “instantaneous” release rate of EtOH into the aqueous layer from the solvent of choice cannot be differentiated. Indeed, we do see this “topping-out effect” with dppb as the ligand (Table 1, entry 14). However, we find that we are able to observe faster catalysts such as [Pd₂(dba)₃] (dba = *trans,trans*-dibenzylideneacetone) by reducing the mole percentage of catalyst (to $\leq 2\%$ in this case). So, while we can circumvent “leveling-effect” issues in the biphasic assay, the need for a viable biphasic and for an acceptable leaving-group release rate into the aqueous layer limits the organic solvents that can be employed in biphasic ISES.
- [27] Restrictions on solvent composition also arise in the IR-thermography (ref. [11a]) and gel-embedded fluorescent-chemosensor (ref. [18b]) screens, in which other practical issues (“bead floatability” and gel swelling, respectively) arise. While a THF:PhCH₃:hexane mixed solvent proved to be best for ISES with this chemistry, for other reactions, in an inverted configuration, it should be possible to run ISES assays with solvents more dense than water.
- [28] As a control experiment, for the cuvette screens of both the Ni⁰- and Mo⁰-catalyzed reactions (Figure 2), aliquots were drawn early from the upper organic layers of the cuvettes. After quenching and extractive workup, NMR spectroscopic analysis using an internal standard (2'-acetonaphthone) showed a ratio of initial rates ([P]/time) of ≈ 7.8 –13:1, which is consistent with the ratio of slopes observed for NADH formation (≈ 8.5 :1) in the aqueous layer of the same cuvettes. Full details of these experiments are provided in the Supporting Information. We simply note here that these experiments are both tedious (one time point is obtained for each aliquot taken, worked up and analyzed by NMR spectroscopy, in contrast to the continuous relative [product] versus time data provided by the ISES screen) and difficult (to obtain a valid time point, one needs an instantaneous quench of the reaction, which may be difficult to obtain, and leads to



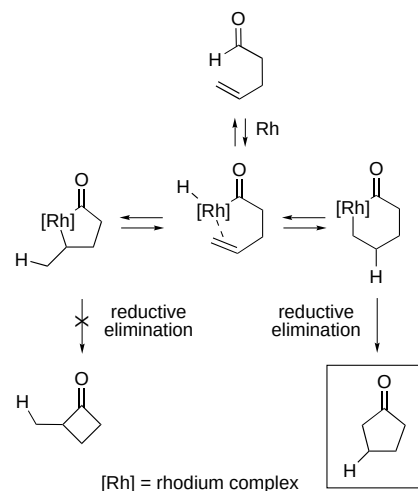
considerable experimental uncertainty, especially for rapid reactions at short time points).

- [29] In light of Evans' work (refs. [23a,b]), one might have expected better results for the Rh^I catalyst here. In fact, whereas the unmodified Wilkinson catalyst proved to be much less efficient than the Ni⁰ catalysts found for this reaction involving a lithiated carbamate as an internal nitrogen nucleophile, it proved to be a good catalyst for the reaction of a simple substrate (allyl ethyl carbonate) with a neutral, external nitrogen nucleophile (dibenzylamine; see the Supporting Information).
- [30] With one exception, all cuvettes contain an organic layer: **1a** (110 μmol), LiHMDS (100 μmol), catalyst (10 mol %), with added PPh₃, where added, in 400 μL total organic solvent (THF:PhMe:hexane 2:1:1), over an aqueous layer containing: NAD⁺ (7.4 mM), ADH (1.3 U) and AIDH (0.12 U; U = the amount of enzyme that leads to the oxidation of 1 μmol of ethanol under the standard assay conditions given in the Supporting Information) in sodium pyrophosphate buffer (15 mM, pH 8.8); final pH 7.7 in 900 μL total aqueous volume. The exception was the [Mo(CO)₃(C₇H₈)]/3PPh₃-catalyzed reaction (Figure 2), which was run at higher catalyst loading (50 mol % catalyst) on substrate **1b**, at half the usual concentration (i. e. 55 μmol in the same volume) for solubility reasons.
- [31] RB-flask reactions contained the same concentrations of **1a** or **1b** and catalyst as the cuvette reactions, with one equivalent LiHMDS in THF:hexane (73:27). All reactions were stopped after 60 min and, where appropriate, the product (**2a** or **2b**) was isolated by SiO₂ chromatography.
- [32] Of the several bases examined for carbamate deprotonation (*n*-BuLi, NaHMDS, KHMDS, LDA, NaOTMS), LiHMDS gave the best amination rates/yields. Interestingly, Evans and co-workers also settled upon this base for his Rh^I-mediated aminations (refs. [23a,b]).
- [33] While Mo⁰-mediated allylic alkylation is well-developed chemistry (For leading references, see: a) O. Belda, N. F. Kaiser, U. Bremberg, M. Larhed, A. Hallberg, C. Moberg, *J. Org. Chem.* **2000**, 65, 5868–5870; b) B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, 121, 10416–10417; c) F. Glorius, A. Pfaltz, *Org. Lett.* **1999**, 1, 141–144), we have been unable to find a report of Mo⁰-mediated allylic amination. Kocovsky et al. have developed a mechanistically distinct Mo^{IV}-mediated allylic-amination reaction upon allylic alcohols (ref. [23i]).
- [34] The PG screens were run at half the usual substrate concentration (138 mM), but at the usual concentrations of Ni(cod)₂ (27.5 mM) and PPh₃ (110 mM). On the other hand, the ligand screens (entries 7–16) were run at the usual concentrations of substrate (275 mM) and metal (27.5 mM), but at half of the typical ligand concentration (55 mM for monodentate ligands or 27.5 mM for bidentate ligands). These changes are apparently approximately compensatory. For example, for the PPh₃ ligand/PMP PG case, the PG-screening conditions gave a rate of 35 mAbs/min, whereas the ligand-screening conditions gave slopes of 36 and 41 mAbs/min, in two independent runs.
- [35] A complete description of these experiments is included in the Supporting Information.
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A Novel Rhodium-Catalyzed Reduction–Oxidation Process: Reaction of 4-Alkynals with Phenol to Provide *cis*-4-Alkenoates**

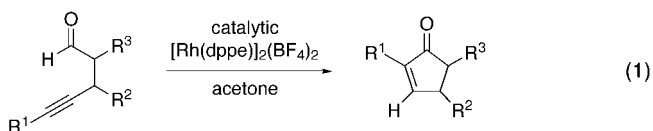
Ken Tanaka and Gregory C. Fu*

For the rhodium-catalyzed intramolecular hydroacylation of a 4-alkenal, five- and six-membered metallacycles have both been shown to be generated during the course of the reaction, although it is the six-membered metallacycle that selectively reductively eliminates to furnish the cyclopentanone product (Scheme 1).^[1–3] We have recently reported that



Scheme 1. Rhodium-catalyzed intramolecular hydroacylation of 4-alkenals to form cyclopentanones.

rhodium complexes also catalyze the corresponding cyclization of a 4-alkynal to afford a cyclopentenone [Eq. (1); dppe = 1,1'-bis(diphenylphosphanyl)ethane], presumably through an analogous six-membered metallacycle (see pathway to **A** in Scheme 2).^[4]

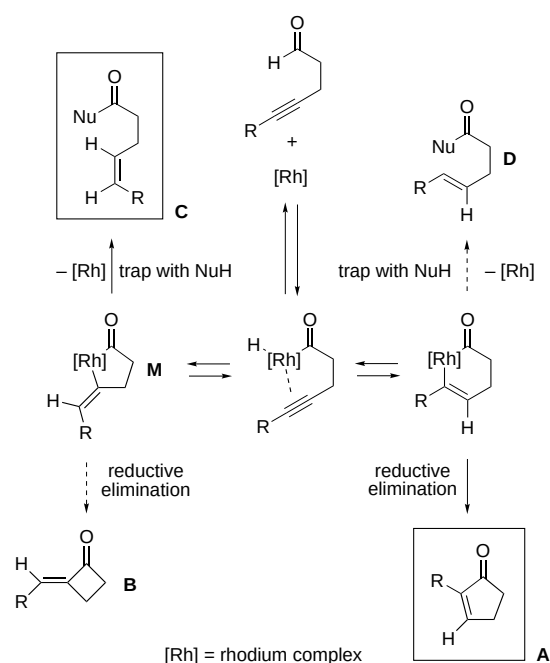


This new catalytic process is mechanistically interesting from several standpoints, including the question of whether a five-membered metallacycle (**M**; Scheme 2) is formed tran-

[*] Prof. Dr. G. C. Fu, Dr. K. Tanaka
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

[**] Support has been provided by Mitsubishi Chemical (postdoctoral fellowship support for K.T.), Bristol-Myers Squibb, Novartis, and Pfizer. Funding for the MIT Department of Chemistry Instrumentation Facility has been provided in part by NSF CHE-9808061 and NSF DBI-9729592.

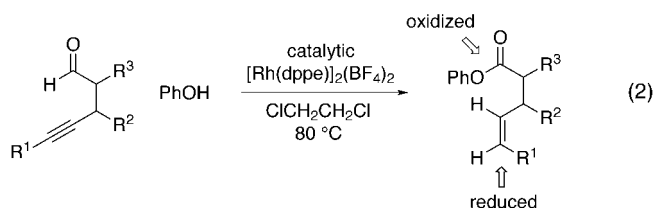
Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.



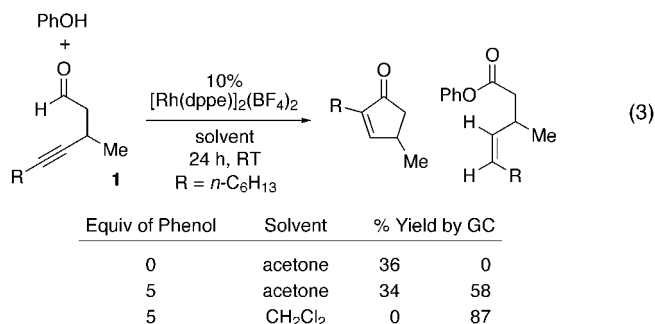
Scheme 2. Rhodium-catalyzed intramolecular hydroacylation of 4-alkynals to form cyclopentenones.

siently under the reaction conditions, as for the cyclization of a 4-alkenal (Scheme 1). We do not observe the generation of strained cyclobutanone **B** (Scheme 2) under the hydroacylation conditions outlined in Equation (1); we anticipated, however, that if we treated the 4-alkynal with $[\text{Rh}(\text{dppe})]_2(\text{BF}_4)_2$ in the presence of a nucleophile (e.g., an alcohol), we might by trapping obtain evidence for the intermediacy of metallacycle **M**.^[5, 6]

The overall transformation achieved by this sequence of events would be an intriguing new rhodium-catalyzed tandem reduction–oxidation: reaction of a 4-alkynal with an alcohol to provide a *cis*-4-alkenoate [see pathway to **C** in Scheme 2; Equation (2)]. Here we report that this novel transformation, which simultaneously effects oxidation of an aldehyde to an ester and reduction of an alkyne to an alkene, can in fact be accomplished in good yield for a range of substrates.



In an initial investigation, we determined that, in contrast to the reaction in the absence of phenol [Eq. (1)], when 4-alkynal **1** is treated with $[\text{Rh}(\text{dppe})]_2(\text{BF}_4)_2$ in acetone in the presence of five equivalents of phenol, the major product is the *cis*-4-alkenoate, rather than the cyclopentenone [Eq. (3)]. Simply by employing dichloromethane, instead of acetone, as the solvent, we can completely eliminate formation of the cyclopentenone [Eq. (3)].^[7] We do not detect the generation of the *trans*-4-alkenoate or the cyclobutanone



under any of these conditions (**D** and **B**, respectively, in Scheme 2).

When we conducted the reaction at higher temperature (80 °C; $\text{ClCH}_2\text{CH}_2\text{Cl}$), the catalyst loading could be lowered to 2.5% $[\text{Rh}(\text{dppe})]_2(\text{BF}_4)_2$. This interesting catalytic tandem reduction–oxidation process can be applied to the reaction of phenol with a wide variety of 4-alkynals to furnish phenyl *cis*-4-alkenoates in good yields (Table 1).^[8, 9] The method tolerates substituents in the β (entry 1) and the α position (entry 2). Furthermore, 1,2-disubstituted (entry 3) as well as 1,2-unsubstituted (entry 4) substrates are suitable reactants.

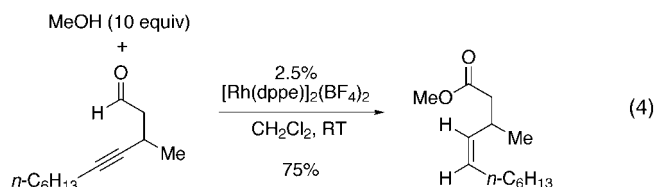
Table 1. Rhodium-catalyzed reactions of 4-alkynals with phenol to form *cis*-4-alkenoates.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			87
2			69
3 ^[c]			76
4 ^[c]			65
5			85
6			95

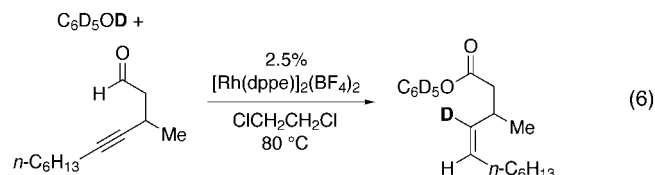
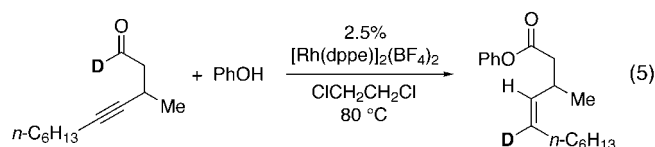
[a] Conditions: 2.5% $[\text{Rh}(\text{dppe})]_2(\text{BF}_4)_2$, PhOH (5 equiv), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 80 °C, 16–65 h. [b] Yields of isolated products, average of two runs. [c] 5% catalyst was used.

Not only alkyl, but also benzyl (entry 5) and trimethylsilyl (entry 6) groups can occupy the 5-position; in the case of the benzyl-substituted alkyne, no isomerization to the styrene derivative is observed.^[10]

Use of methanol, rather than phenol, as the nucleophile, also leads to tandem reduction–oxidation of the 4-alkynal in good yield [Eq. (4)].^[11]



Our preliminary mechanistic data are consistent with the pathway for formation of *cis*-4-alkenoate **C** that is outlined in Scheme 2. For example, we have established that the aldehyde hydrogen (deuterium) atom of the starting material migrates stereospecifically and exclusively to the 5-position of the product [Eq. (5)].^[12] Furthermore, the oxygen-bound hydrogen (deuterium) atom of phenol is transferred cleanly to the 4-position [Eq. (6)].



In conclusion we have developed an unprecedented rhodium-catalyzed transformation in which an alcohol reacts with a 4-alkynal to furnish a *cis*-4-alkenoate in good yield. This novel tandem process couples the reduction of an alkyne to an alkene with the oxidation of an aldehyde to an ester. Our mechanistic data are consistent with a five-membered rhodium metallacycle as a key intermediate in the catalytic cycle. Future work will focus on additional studies of the reaction pathway, as well as on the exploitation of metallacycles in other interesting transformations.

Received: February 8, 2002 [Z18674]

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- [3] For the isolation of a *cis*-hydridopent-4-enoylrhodium(III) complex, see: D. Milstein, *J. Chem. Soc. Chem. Commun.* **1982**, 1357–1358.
- [4] K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2001**, 123, 11492–11493.
- [5] For rhodium-catalyzed cyclizations of 4-alkenals, the issue of reversible formation of a five-membered metallacycle was addressed through deuterium labeling/scrambling studies (ref. [2]). Unfortunately, this approach cannot be applied to the corresponding reactions of 4-alkynals.
- [6] The reaction of acylrhodium species with nucleophiles is, of course, precedented. For example, see: a) Monsanto acetic acid process (I[−] as the nucleophile). Leading references: J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**, Chapt. 12.6; b) phenol as the nucleophile: M. Murakami, T. Tsuruta, Y. Ito, *Angew. Chem.* **2000**, 112, 2600–2602; *Angew. Chem. Int. Ed.* **2000**, 39, 2484–2485.
- [7] At room temperature in THF, benzene, and CH₃CN, we observe no reaction when 4-alkynal **1** is treated with [Rh(dppe)]₂(BF₄)₂.
- [8] Notes: a) Among the ligands that we have surveyed (e.g., dcpe, dppe, and BINAP), dppe provides the cleanest and the fastest reactions; b) with less than five equivalents of phenol, we obtain a somewhat lower yield of product. With more than five equivalents of phenol, we observe a slower reaction.
- [9] Sample experimental (Table 1, entry 1): In the air, [Rh(dppe)]₂(BF₄)₂ (16 mg, 0.013 mmol) was placed into a Schlenk tube, which was then filled with argon. Under a positive pressure of argon, a solution of PhOH (260 mg, 2.76 mmol) and 3-methylundec-4-ynal (100 mg, 0.555 mmol) in ClCH₂CH₂Cl (5 mL) was added. The vessel was closed, and the mixture was stirred at 80 °C for 40 hours. The resulting solution was concentrated and purified by column chromatography (pentane:Et₂O = 20:1), which furnished phenyl (*Z*)-3-methylundec-4-enoate (131 mg, 0.477 mmol, 86%) as a colorless oil.
- [10] For the reaction of 3-methyl-5-(1-cyclohexenyl)pentyn-4-ol, we obtain a modest yield of the *cis*-4-alkenoate (38%), because of the formation of a significant quantity of the cyclopentenone.
- [11] With water as the nucleophile in acetone, we obtain a 53% yield of the target carboxylic acid. Use of a hindered alcohol results in the formation of an acetal as well as the desired ester.
- [12] In a preliminary kinetic study, we observed *k*_H(CHO)/*k*_D(CDO) ≈ 1.0 at 80 °C.

[1] For examples of rhodium-catalyzed cyclizations of 4-alkenals to cyclopentanones, see: a) K. Sakai, J. Ide, N. Nakamura, *Tetrahedron Lett.* **1972**, 1287–1290 (stoichiometric [Rh(PPh₃)₃Cl]); K. Sakai, Y. Ishiguro, K. Funakoshi, K. Ueno, H. Suemune, *Tetrahedron Lett.* **1984**, 25, 961–964; b) C. F. Lochow, R. G. Miller, *J. Am. Chem. Soc.* **1976**, 98, 1281–1283; c) R. C. Larock, K. Oertle, G. F. Potter, *J. Am. Chem.*

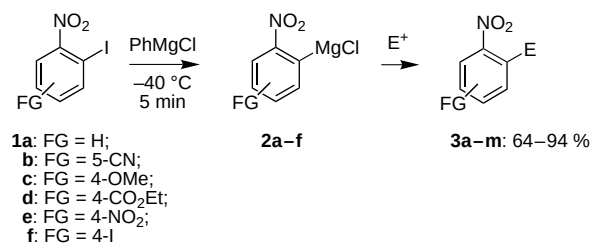


General Preparation of Functionalized *o*-Nitroarylmagnesium Halides through an Iodine–Magnesium Exchange**

Ioannis Sapountzis and Paul Knochel*

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

The preparation of functionalized organometallic compounds is an important research field since it allows the formation of new C–C bonds between polyfunctional nucleophiles and electrophiles, leading to multifunctional products.^[1] Although organozinc compounds have proved to be very useful, the recent use of the I–Mg exchange allows the straightforward synthesis of various highly functionalized aryl-,^[2] heteroaryl-,^[3] and alkenylmagnesium^[4] reagents. Nitro groups are present in many important aromatic compounds,^[5] but have been regarded as being incompatible with organometallic species.^[6] Only scarce examples of nitro-substituted aryl organometallic compounds have been reported.^[7] Herein we wish to report that the I–Mg exchange allows an efficient preparation of polyfunctional arylmagnesium reagents that bear a nitro group *ortho* to the iodine atom. Furthermore, we will show that this new class of organomagnesium compounds is compatible with several transition metal catalyzed cross-coupling reactions. In a preliminary experiment, we treated 2-iodonitrobenzene (**1a**) with phenylmagnesium chloride (1.1 equiv) in THF at –40 °C. Within 5 min, a complete I–Mg exchange was observed, as indicated by GC analysis of reaction aliquots. The resulting nitro-substituted Grignard reagent (**2a**) reacted with benzaldehyde (1.2 equiv) within 0.5 h at –40 °C to give the expected benzhydryl alcohol (**3a**) in 87 % yield (Scheme 1 and Table 1, entry 1).



Scheme 1. Preparation of *o*-nitro substituted arylmagnesium reagents.

Interestingly, the use of other more reactive Grignard reagents such as MeMgX or *i*PrMgCl for the I–Mg exchange led to complex reaction mixtures. These organometallic reagents clearly react with the nitro functional group. The

Table 1. Products of the reaction of the functionalized nitro-substituted arylmagnesium compounds **2** with electrophiles.

Entry	Grignard reagent	Electrophile	3	Yield [%] ^[a]
1		PhCHO		87
2	2a	allyl bromide		75 ^[b]
3		PhCHO		94
4		PhCHO		72
5	2c			72 ^[b]
6		PhCHO		94
7	2d	cHexCHO		64
8	2d			75 ^[b]
9	2d	PhCOBr		76 ^[b]
10		PhCHO		81
11	2e	cHexCHO		74
12		PhCHO		89
13	2f			74 ^[b]

[a] Yield of isolated analytically pure product. [b] The Grignard reagent was transmetalated with CuCN·2LiCl before reaction with the electrophile.

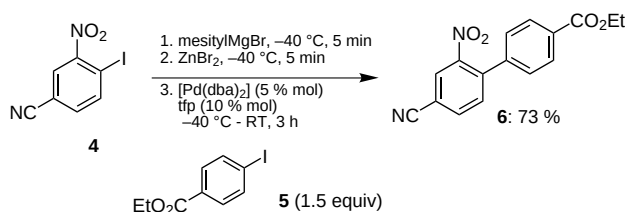
[*] Prof. Dr. P. Knochel, Dipl.-Chem. I. Sapountzis
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49)89-2180-76 80
E-mail: paul.knochel@cup.uni-muenchen.de

[**] We thank the Deutsche Forschungsgemeinschaft (Leibniz program) for financial support. I.S. thanks Aventis Pharma (Frankfurt a.M.) for a fellowship. We also thank Chemetall GmbH (Frankfurt a.M.) and BASF AG (Ludwigshafen) for generous gifts of chemicals.

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

use of *meta*- or *para*-substituted iodonitrobenzenes also gave rise to mixtures of products. In these cases, the nitro functionality also reacts with PhMgCl .^[7] However, a variety of functional groups including ester, cyano, and methoxy groups, and other nitro or iodo functionalities are tolerated, thus allowing the synthesis of a broad range of functionalized *ortho*-nitro-substituted arylmagnesium species **2a–f**, which give aliphatic and aromatic alcohols in excellent yields (Table 1, entries 1, 3, 4, 6, 7, 10–12). Remarkably, in the case of 2,5-diiodonitrobenzene (**1f**), only the *ortho*-iodine atom undergoes I–Mg exchange to give the alcohol **3l** in 89% yield after reaction with benzaldehyde (Table 1, entry 12). This selectivity can be explained by a chelation effect of the nitro functionality. Its inductive effect should also favor the *ortho*-iodine–magnesium exchange. Amazingly, a fast I–Mg exchange was also observed for 2,5-dinitroiodobenzene (**1e**). In this case, the I–Mg exchange was complete within 30 s at -40°C . A smooth reaction is observed with aldehydes, despite the presence of two nitro groups in the Grignard reagent **2e**, leading to the alcohols **3j** and **3k** in 81% and 74% yields, respectively (Table 1, entries 10 and 11).

The reactivity and selectivity of the Grignard reagents of type **2** is not always appropriate for reactions with all electrophiles. In some cases, transmetalation with a transition metal salt is required. Thus, for the reaction with allylic halides or acid halides the intermediate *o*-nitroarylmagnesium reagent is treated with $\text{CuCN} \cdot 2\text{LiCl}$ ^[8] (1 equiv, -40°C , 5 min), resulting in the formation in situ of an arylcopper species, which can be smoothly allylated (Table 1, entries 2, 5, 8 and 13) and benzoylated with benzoyl bromide (Table 1, entry 9). Similarly, a Pd^0 -catalyzed Negishi cross-coupling reaction^[9] is possible upon transmetalation of the Grignard reagent with ZnBr_2 to give the corresponding organozinc reagent (Scheme 2).



Scheme 2. Negishi cross-coupling reaction of 4-iodo-3-nitrobenzonitrile **4**.

In this case, it is advantageous to perform the I–Mg exchange of **4** with the sterically hindered mesitylmagnesium bromide.^[10] After transmetalation of the Grignard reagent with ZnBr_2 , ethyl 4-iodobenzoate (**5**) is added in the presence of $[\text{Pd}(\text{dba})_2]$ (5 mol %; dba = *trans,trans*-dibenzylideneacetone) and tri-*o*-furylphosphane (tfp, 10 mol %). The cross-coupling reaction proceeds smoothly between -40°C and room temperature to afford the polyfunctional product **6** in 73% yield (Scheme 2).

In summary, we have shown that the I–Mg exchange reaction allows the preparation of a variety of new functionalized *ortho*-nitro arylmagnesium reagents, thus expanding the scope of these organometallic compounds for applications in organic synthesis.

Experimental Section

Typical procedure (**3f**): A dry argon-flushed 25-mL flask, equipped with a magnetic stirrer and a septum, was charged with ethyl 4-iodo-3-nitrobenzoate (642 mg, 2 mmol). Dry THF was added, the mixture was cooled to -40°C , and PhMgCl (1.1 mL, 2 M in THF, 2.2 mmol) was then added dropwise. The I–Mg exchange was complete after 5 min (checked by GC analysis of reaction aliquots). Benzaldehyde (254 mg, 2.4 mmol) was added to the Grignard benzoate **2d**. The reaction mixture was stirred for 0.5 h at -40°C , and then quenched with a saturated solution of NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (2×40 mL), and the organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (dichloromethane) to yield the benzylic alcohol **3f** as a pale yellow oil (568 mg, 94%).

Received: January 30, 2002 [Z18611]

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A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations**

Wenjun Tang and Xumu Zhang*

The design and synthesis of chiral phosphane ligands have played a significant role in the development of efficient transition metal catalyzed reactions. Catalytic asymmetric hydrogenation, as one of the most practical and efficient methods for the synthesis of chiral building blocks, has attracted much attention in both academia and industry.^[1] Although excellent enantioselectivities have been obtained by using chiral bisphosphane ligands such as DIPAMP,^[2] DIOP,^[3] Chiraphos,^[4] Norphos,^[5] BPPM,^[6] DEGphos,^[7] BINAP,^[8] DuPhos,^[9] BPE,^[9] BICP,^[10] SpirOP,^[11] PennPhos,^[12] BisP*,^[13] MiniPhOS,^[14] Binaphane,^[15] and PHANEPHOS,^[16] the search for more practical and efficient ligands in terms of ease of preparation, high enantioselectivity, and high turnover number (TON) remains an important goal in asymmetric hydrogenation. Herein we report the synthesis and application of a new chiral 1,2-bisphospholane ligand, (1*S*,1'*S*,2*R*,2'*R*)-1,1'-di-*tert*-butyl-[2,2']-diphospholanyl (**1**; abbreviated (1*S*,1'*S*,2*R*,2'*R*)-TangPhos, Figure 1) in highly effi-

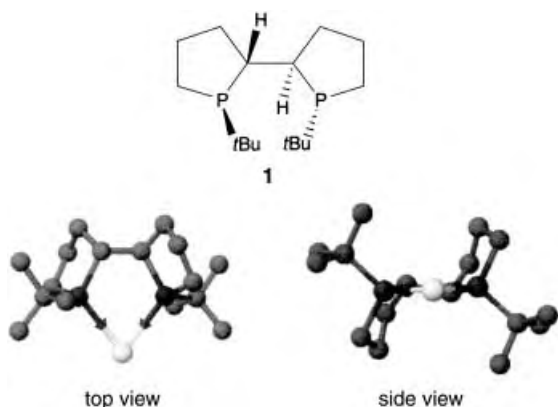


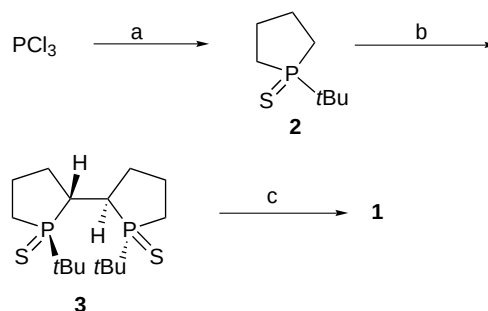
Figure 1. MM2 Calculations of the Rh-TangPhos complex based on the CAChe program.

cient rhodium-catalyzed asymmetric hydrogenation of α -(acylamino)acrylic acids, α -(acylamino)acrylic esters, and α -arylenamides. The ligand contains four stereogenic centers: two carbon and two phosphorus centers. This structural motif is different from axially dissymmetric BINAP, bisphosphanes with two stereogenic centers (e.g. Chiralphos), and bisphosphanes with two stereogenic phosphorus centers (e.g. DIPAMP and BisP*). We hypothesized that the two five-

membered phospholane rings in the backbone of **1** restrict its conformational flexibility, which could lead to high enantioselectivity in asymmetric reaction.

The importance of the conformational properties of a Rh-ligand complex in determining enantioselectivity has been well recognized. In general, ligands with rigid backbones are preferred for achieving high enantioselectivities. Imamoto's BisP* is a good ligand for asymmetric hydrogenation.^[13] However, BisP* contains two methylene groups in the backbone and its five-membered ring metal ligand complex is conformationally flexible. We reasoned that the Rh-TangPhos complex should have a well-defined rigid conformation through two additional five-membered rings on the backbone. Molecular modeling (Figure 1) showed that the Rh-TangPhos complex exhibits a similar but more rigid chiral environment than the Rh-BisP* complex.

Ligand **1** was prepared in three steps from readily accessible materials by using phosphane sulfides as intermediates (Scheme 1).^[17] Phosphane sulfide **2** was directly prepared from phosphorus chloride in one step with three operations.



Scheme 1. Synthesis of **1**. Reagents and conditions: a) *t*BuMgCl, BrMg(CH₂)₂MgBr, S, 45 %; b) *n*BuLi, (–)-sparteine, CuCl₂, recrystallization, 20 %; c) hexachlorodisilane, benzene, 88 %.

Selective deprotonation of **2** by an *n*BuLi-(–)-sparteine complex followed by a Cu-mediated oxidative coupling afforded the C₂-symmetric bisphosphane sulfide **3** with 95 % *ee*, along with the formation of the *meso* compound (C₂:*meso* 83:17). Recrystallization afforded optically pure **3** in 20 % yield. The configuration at the P atom of **3** was assigned by comparison with the structure of BisP*,^[18] the relative stereochemistry of the carbon and phosphorus centers was assigned based on a known compound.^[19] Desulfuration of **3** by hexachlorodisilane^[20] afforded white air-sensitive crystalline solid **1** ((1*S*,1'*S*,2*R*,2'*R*)-TangPhos) in 88 % yield.

α -(Acylamino)acrylic acids and esters were hydrogenated in methanol at room temperature under hydrogen (20 psi). The catalyst was formed in situ from [Rh(nbd)₂]SbF₆ (nbd = 3,5-norbornadiene) and bisphosphane **1** (1:1.1). As shown in Table 1, a wide array of ring-substituted phenylalanine derivatives were formed with extremely high enantioselectivities. It is noted that almost 100 % *ee* values were obtained in the hydrogenation of both α -(acylamino)acrylic acids and their esters. The catalyst can tolerate thio- and halogen groups. The 2-naphthyl (Table 1, entries 13 and 14) as well as the *N*-benzoyl derivatives (Table 1, entries 15 and 16) were also hydrogenated with high enantioselectivities (> 99 % *ee*).

[*] Prof. X. Zhang, W. Tang
Department of Chemistry, The Pennsylvania State University
University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

[**] This work was supported by the National Institutes of Health.

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

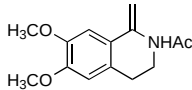
Table 1. Rh-catalyzed asymmetric hydrogenation of α -(acylamino)acrylic acid derivatives.^[a]

$\text{Ar}-\text{CH}=\text{CH}-\text{COOR} + \text{H}_2 \xrightarrow[\text{CH}_3\text{OH}, 12 \text{ h, RT}]{[\text{Rh}(\text{nbd})_2]\text{SbF}_6 \text{ (1 mol\%)} \text{ 1 (1.1 mol\%)}} \text{Ar}-\text{CH}_2-\text{CH}(\text{NHAc})-\text{COOR}$				
Entry	4	Ar	R	ee [%] ^[b]
1	a	Ph	H	> 99
2	b	Ph	CH ₃	99
3	c	<i>p</i> -FPh	H	> 99
4	d	<i>p</i> -FPh	CH ₃	> 99
5	e	<i>p</i> -MeOPh	H	> 99
6	f	<i>p</i> -MeOPh	CH ₃	> 99
7	g	<i>m</i> -BrPh	H	> 99
8	h	<i>m</i> -BrPh	CH ₃	> 99
9	i	<i>o</i> -ClPh	H	> 99
10	j	<i>o</i> -ClPh	CH ₃	> 99
11	k	2-thienyl	H	> 99
12	l	2-thienyl	CH ₃	> 99
13	m	2-naphthyl	H	> 99
14	n	2-naphthyl	CH ₃	> 99
15	o	Ph	H, <i>N</i> -Bz	> 99
16	p	Ph	CH ₃ , <i>N</i> -Bz	> 99

[a] See Experimental Section for details. [b] The *R* absolute configuration was assigned by comparison of the optical rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chiralsil-VAL III FSOT) or Chiral HPLC (Chiralcel OJ). The *ee* values of the acids were determined on the corresponding methyl ester.

α -Arylenamides were also hydrogenated with the Rh–TangPhos catalyst. As shown in Table 2, a variety of α -arylenamides were hydrogenated to form chiral amides with excellent enantioselectivities. Enantiomeric excesses of more than 99% were observed in the hydrogenation of α -phenyl-

Table 2. Rh-catalyzed asymmetric hydrogenation of α -arylenamides.^[a]

$\text{Ar}-\text{CH}=\text{CH}-\text{NHAc} + \text{H}_2 \xrightarrow[\text{CH}_3\text{OH}, \text{H}_2 (20 \text{ psi}), 12 \text{ h, RT}]{[\text{Rh}(\text{nbd})_2]\text{SbF}_6 \text{ (1 mol\%)} \text{ 1 (1.1 mol\%)}} \text{Ar}-\text{CH}_2-\text{CH}(\text{NHAc})-\text{R}$				
Entry	6	Ar	R	ee [%] ^[b]
1	a	Ph	H	> 99
2	b	<i>m</i> -MePh	H	> 99
3	c	<i>p</i> -CF ₃ Ph	H	> 99
4	d	<i>p</i> -CyPh	H	> 99
5	e	<i>p</i> -PhPh	H	99
6	f	2-naphthyl	H	> 99
7	g	Ph	CH ₃	98
8	h	<i>p</i> -CF ₃ Ph	CH ₃	98
9	i	<i>p</i> -MeOPh	CH ₃	98
10	j	2-naphthyl	CH ₃	99
11	k	Ph	CH(CH ₃) ₂	98
12	l	Ph	CH ₂ Ph	99
13	m			97

[a] See Experimental Section for details. Enamides **6** were prepared according to the literature method. For the *E/Z* ratio of **6g–l**, see references [10b, 21]. [b] The *R* absolute configuration was assigned by comparison of the optical rotation with reported data. Enantiomeric excesses were determined by chiral GC on a Supelco Chiral Select 1000 column or by chiral HPLC on a (*R,R*)-Poly Whelk-01 column.

enamides, regardless of the substituents on the phenyl ring (Table 2, entries 1–5). Hydrogenation of a 2-naphthyl derivative also gave an excellent *ee* value (Table 2, entry 6). For β -substituted isomeric enamide mixtures (*Z/E*) and β -methyl-substituted enamides with various substituents on the 1-aryl group, high *ee* values were also obtained, regardless of the various β -substituents or the electronic properties of the 1-aryl group (Table 2, entries 7–12). Asymmetric hydrogenation of *N*-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroquinoline proceeded smoothly, yielding (*R*)-(–)-*N*-acetylsalsolidine in quantitative yield and with 97% *ee*. The enantioselectivities of the hydrogenation of enamides with the Rh–TangPhos system are comparable or higher than those observed with the Rh–DuPhos system.^[21]

To evaluate further the catalytic efficiency of Rh–TangPhos system in asymmetric hydrogenations, the catalyst precursor [Rh(nbd)(**1**)]SbF₆ was prepared. Hydrogenation of methyl α -(acetylamino)-2-phenylacrylate in the presence of [Rh(nbd)(**1**)]SbF₆ (0.01 mol %, 10000 TON) afforded (*R*)-methyl 2-acetylamino-3-phenylpropionate in 100% yield and with 99.8% *ee*. High turnovers (10000) were also observed in the hydrogenation of *N*-acetyl-1-phenylethanamine, yielding *N*-acetyl-1-phenylethylamine in 100% yield and with 99.3% *ee*.

In conclusion, we have designed and synthesized a new chiral 1,2-bisphospholane ligand TangPhos (**1**) in a three-step synthetic route. This readily accessible ligand is potentially practical for the Rh-catalyzed asymmetric hydrogenation of α -(acylamino)acrylic acids and α -arylenamides. Further applications of the ligand in asymmetric catalysis are in progress.

Experimental Section

1: Hexachlorodisilane (3.25 mL, 5.08 g, 18.9 mmol) was added dropwise to a solution of **3**^[22] (440 mg, 1.26 mmol) in benzene (25 mL). The mixture was stirred at reflux for 4 h. After the solution was cooled to room temperature, degassed NaOH solution (50 mL, 30% w/w) was slowly added to the reaction mixture in an ice-water bath. The resulting mixture was then stirred at 60 °C until the aqueous layer became clear. The two phases were separated. The water phase was washed twice with degassed benzene (2 × 30 mL). The combined benzene layers were dried over Na₂SO₄ and concentrated. The solid residue was redissolved in a minimum amount of degassed dichloromethane, which was subsequently passed through a basic Al₂O₃ plug (eluent: Et₂O:Hexane 1:10) to give pure crystalline **1** (320 mg, 88%). ¹H NMR (360 MHz, CD₂Cl₂): δ = 1.01 (d, ³J_{HP} = 11.5 Hz, 18H), 1.64 (m, 8H), 1.87 (m, 2H), 2.00 (m, 2H), 2.25 ppm (m, 2H); ¹³C NMR (90 MHz, CD₂Cl₂): δ = 23.6 (t, ²J_{CP} = 6.6 Hz), 28.5 (dd, ²J_{CP} = 7.0, 7.5 Hz), 28.8, 28.9, 34.6 (t, ²J_{CP} = 5.1 Hz), 42.9 ppm (m); ³¹P NMR (145 MHz, CD₂Cl₂): δ = 14.5 ppm; APCI MS: 287 [M⁺ + H]; HRMS calcd for C₁₆H₃₃P₂: 287.2058, found: 287.2035.

[Rh(nbd)(**1**)]SbF₆: A solution of (1*S*,1*S'*,2*R*,2*R'*)-TangPhos (**1**, 57 mg, 0.2 mmol) in THF (1 mL) was added dropwise to a solution of [Rh(nbd)₂]SbF₆ (104 mg, 0.2 mmol) in degassed THF (1 mL) at –10 °C. The resulting mixture was stirred at ambient temperature for 15 min. Degassed diethyl ether (12 mL) was then added to the vigorously stirred solution. The resulting dark brown precipitate was filtered, further washed with diethyl ether (3 × 10 mL), and dried under vacuum. Yield: 80 mg, 56%. ¹H NMR (360 MHz, CD₂Cl₂): δ = 1.05 (d, ³J_{HP} = 7.2 Hz, 18H), 1.56 (m, 2H), 1.73 (m, 2H), 1.86 (s, 2H), 1.99 (m, 2H), 2.21 (m, 4H), 2.38 (m, 4H), 4.15 (s, 2H), 5.56 (s, 2H), 5.70 ppm (s, 2H); ³¹P NMR (145 MHz, CD₂Cl₂): δ = 101.1 ppm (d, ²J_{RP} = 151.6 Hz); ESI MS: 481 [M – SbF₆[–]]; HRMS calcd for C₂₃H₄₀P₂Rh: 481.1660, found 481.1627.

General hydrogenation procedure: (1*S*,1*S'*,2*R*,2*R'*)-TangPhos (**1**, 0.10 mL, 0.05 M solution in methanol, 0.005 mmol) was added to a solution of

[Rh(nbd)₂]₂SbF₆ (2.3 mg, 0.0045 mmol) in methanol (3 mL) in a glovebox. After the mixture was stirred for 10 min, the substrate (0.5 mmol) was added. The hydrogenation was performed at room temperature under H₂ (20 psi) for 12–48 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica-gel plug to remove the catalyst. The resulting solution was used directly for chiral GC or HPLC to measure the enantiomeric excess. For the hydrogenation of dehydroamino acids, the enantiomeric excesses were measured after conversion into their corresponding methyl esters by treatment with TMSCHN₂ (TMS = trimethylsilyl).

Received: February 4, 2002 [Z18637]

Helical Chiral Polymers without Additional Stereogenic Units: A New Class of Ligands in Asymmetric Catalysis**

Michael Reggelin,* Melanie Schultz, and Michael Holbach

Soluble polymers may be promising ligands in transition metal catalysis for a number of reasons. The reisololation of the chiral catalyst by precipitation or ultrafiltration should be easy, and all the analytical and kinetic advantages of a reaction in homogenous phase should be maintained. If the polymer is chiral and nonracemic, asymmetric induction can be expected, and finally, a number of beneficial effects related to the macromolecular state of the system may allow for the synthesis of novel ligands with properties not achievable with micromolecules. These effects include, for example, cooperativity and chiral amplification as observed in polyisocyanates.^[1]

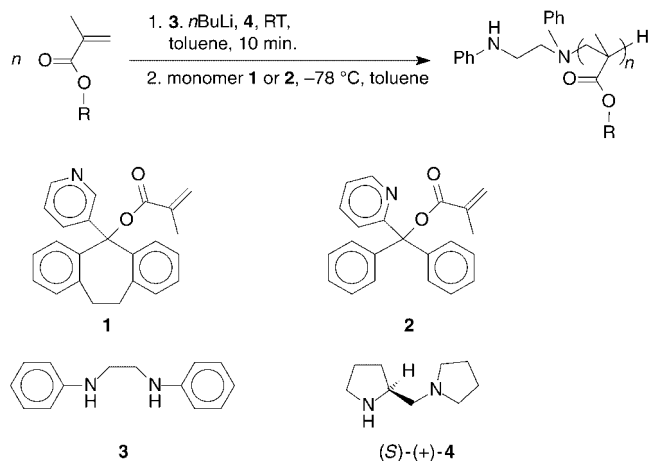
The most obvious way to prepare a polymeric chiral soluble ligand is to attach only one metal binding site per polymer chain. This was rather successful in the asymmetric dihydroxylations described by Bolm et al.^[2] and Janda et al.^[3] The major disadvantage of this approach is the very low density of reactive centers per unit mass. To improve this situation it is necessary to prepare multiple-site polymeric catalysts with uniform microenvironments. The polybinaphthols prepared by Pu et al. appear to be successful examples of this strategy.^[4] The remaining problems with these ligands include the necessity to prepare the enantiomerically pure monomers and the question of contraproductive interactions of the different sources of chirality (planar chirality of the monomers and helical chirality of the polymer). Indeed, we think that for the phosphane-modified helical chiral dodecapeptides developed by Gilbertson et al.^[5] the major reason for the failure to achieve good enantioselectivities in asymmetric hydrogenation reactions is such a contraproductive interaction between the centrochirality of the constituting amino acids and the helical secondary structure. Facing this situation we felt it would be best to erase all sources of chirality except the helicity of a stereoregular and configurationally stable polymer containing donor atoms such as nitrogen or phosphorus.

We followed the work of Okamoto et al.^[6, 7] and prepared two chiral polymers by helix-sense selective anionic polymerization of sterically congested methacrylates by using a chiral nonracemic base mixture as initiator (Scheme 1, Table 1). The chiral initiator was prepared by mixing either (+)- or (–)-1-(2-pyrrolidinomethyl)pyrrolidine ((S)- or (R)-**4**) and the diamine **3** with one equivalent of *n*BuLi at room temperature in toluene. This mixture was added to solutions of the monomers **1** and **2** so that the monomer/initiator ratio was

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[*] Prof. Dr. M. Reggelin, Dipl.-Chem. M. Schultz, M. Holbach
Institut für Organische Chemie
Technische Universität Darmstadt
Petersenstrasse 22, 64287 Darmstadt (Germany)
Fax: (+49) 6151-16-5531
E-mail: re@oc.chemie.tu-darmstadt.de

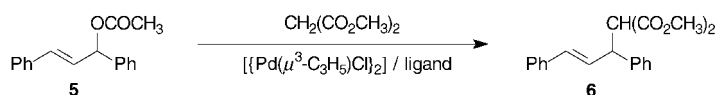
[**] We thank Degussa AG for generous gifts of transition metal salts.



Scheme 1. Helix sense selective polymerization of methacrylates **1** and **2** with the additives **3** and **4**.

15:1. After the reaction times compiled in Table 1, the resulting polymers were isolated following published procedures.

To explore the suitability of these polymers as chiral ligands in asymmetric C–C bond forming processes we chose the palladium catalyzed allylic substitution reaction with 1,3-diphenylprop-2-enyl acetate as substrate and dimethyl malonate (DMM) as nucleophile (Scheme 2, Table 2).^[8–11] First, we



Scheme 2. Allylic substitution of 1,3-diphenylprop-2-enyl acetate (**5**) catalyzed by palladium complexes generated in situ.

looked for potential catalytic activity of the nitrogen-containing compounds **3** and **4** used in the anionic polymerization. Especially the former was of interest, because it is incorporated into the polymer as the end group. Entries 1 and 2 show that **3** does not catalyze the reaction at all. On the contrary, (+)-**4** is active and produces (*R*)-**6** with a slight enantiomeric excess of about 10%. For that reason we meticulously purified the polymers to avoid any contamination with this chiral diamine (checked by ^1H NMR spectroscopy and gel permeation chromatography (GPC)). Next, we looked for the catalytic activity of the monomers and found that only **1** is active and furnishes **6** with 57% yield (entries 4–7).

After this preparatory work we tried to prepare Pd complexes from the polymers. In a typical experiment we

Table 2. Allylic alkylations of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.^[a]

Entry	Ligand ^[a]	[Pd] [mol %] ^[b]	Solvent	<i>T</i> [$^{\circ}\text{C}$]	<i>t</i> [h]	Yield [%] ^[c]	<i>ee</i> [%] ^[d]	Config. ^[e]
1	3	10	CH_2Cl_2	25	48	0	–	–
2	3	10	CH_2Cl_2	40	14	0	–	–
3	(+)- 4	10	CH_2Cl_2	25	14	65 ^[f]	9.9	<i>R</i>
4	2	10	CH_2Cl_2	40	90	0	–	–
5	2	25	CH_2Cl_2	40	40	0	–	–
6	1	10	CH_2Cl_2	40	90	48	0	–
7	1	25	CH_2Cl_2	40	40	57	0	–
8	(+)-poly- 2	10	CH_2Cl_2	25	72	0	–	–
9	(+)-poly- 2	10	CH_2Cl_2	40	72	0	–	–
10	(+)-poly- 2	10	THF	60	14	0	–	–
11	(+)-poly- 2	10	C_6H_6	80	14	0	–	–
12	(+)-poly- 1	10	CH_2Cl_2	25	72	12	29	<i>R</i>
13	(+)-poly- 1	25	CH_2Cl_2	25	72	66 ^[f]	33	<i>R</i>
14	(+)-poly- 1	10	CH_2Cl_2	40	48	74	27	<i>R</i>
15	(+)-poly- 1	25	CH_2Cl_2	40	14	79 ^[f]	32	<i>R</i>
16	(+)-poly- 1	10	CH_2Cl_2	40	70	88 ^[f]	28	<i>S</i>
17	(+)-poly- 1	25	CH_2Cl_2	40	40	81 ^[f]	33	<i>S</i>
18	<i>rac</i> -poly- 1	10	CH_2Cl_2	40	70	92 ^[f]	0	–
19	<i>rac</i> -poly- 1	25	CH_2Cl_2	40	40	78 ^[f]	0	–

[a] 24 mol % repeating unit (based on substrate 1,3-diphenylprop-2-enyl acetate) or 60 mol % in experiments with 10 or 25 mol % Pd, respectively. [b] Based on substrate. [c] Yields of isolated product. [d] Determined by ^1H NMR in the presence of 20 mol % of the chiral shift reagent $[\text{Eu}(\text{hfc})_3]$, hfc = 3-(heptafluoropropyl-hydroxymethylene)-D-camphorate. [e] By comparison with reference [12]. [f] Quantitative conversion according to TLC.

mixed 27.2 mg (84 μmol monomeric units) of poly-**2** and 6.4 mg (17.5 μmol) of dimeric $[\text{Pd}(\mu^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ in CH_2Cl_2 at room temperature. After one hour 88 mg (350 μmol) of the substrate and 139 mg (1.05 mmol) of DMM were added. This corresponded to 10 mol % Pd and a [N]:[Pd] ratio of 2.4:1 which reflects our initial assumption that a bidentate complex involving two consecutive turns of the helix might be formed. Not unexpectedly after our experience with the monomer **2**, no reaction with the substrate (Table 2, entries 8–11) could be observed. Although a negative result at first sight, these experiments confirm the complete absence of any residual **4** and any interference of the nitrogen-containing end group (see above).

We suspected the nitrogen atom in poly-**2** is not accessible enough to be complexed by palladium and therefore hoped that the situation would be improved when the nitrogen atom is in the 3-position in the pyridine ring. This was indeed the case. As already stated the monomer **1** is an active catalyst (Table 2, entries 6 and 7), and to our delight this was also true for the polymer (+)-poly-**1** (entries 12–15). Moreover, we found a significant enantiomeric enrichment in the resulting

Table 1. Helix sense selective polymerization of methacrylates **1** and **2**.^[a]

Entry	Monomer ^[b]	Polymer ^[c]	Initiator ^[c]	<i>t</i> [h]	Yield [%] ^[d]	DP ^[e]	M_w/M_n ^[f]	Tacticity ^[f]	$[\alpha]_{365}^{25}$ ^[g]
1	2	(+)-poly- 2	(+)- 4	4	89	40	1.15	> 99	+ 1452
2	1	(+)-poly- 1	(+)- 4	43	34	27	1.19	> 99	+ 1385
3	1	(+)-poly- 1	(+)- 4	48	59	34	1.12	> 99	– 1475
4	1	<i>rac</i> -poly- 1	<i>rac</i> - 4	48	50	37	1.21	> 99	0

[a] All polymerizations were carried out with 1.0 g of monomer in toluene at -78°C . The monomer: initiator ratio was 15:1. [b] The monomer structure corresponds to R in Scheme 1. [c] For abbreviations see Figure 1. [d] Fraction insoluble in methanol and benzene/hexane. [e] DP = degree of polymerization. Determined by GPC (poly(methyl methacrylate) (PMMA) standard) after acidic hydrolysis and conversion to PMMA. [f] Determined by ^1H NMR analysis of the derived PMMA. [g] $c = 1.0$, CHCl_3 :2,2,2-trifluoroethanol (9:1 by volume).

substitution product **6** (27–33% *ee*). With 10 mol% Pd at 40 °C the reaction was virtually quantitative as judged by TLC. The yields of isolated products were somewhat lower and variable because of the very small amounts handled in these initial experiments. The major enantiomer formed in the experiments with the polymer derived from the (+)-**4**-containing initiator mixture was *R*-configured. To verify our expectation that the product configuration would be inverted when the configuration of the catalyst is inverted, we repeated the experiment with the polymer having the opposite helical sense (entries 16 and 17). As expected we now obtained (*S*)-**6** in very high yield and with the same *ee*.

Finally, we used *rac*-poly-**1** obtained by polymerization with *rac*-**4/3**-*n*BuLi as initiator. This time *rac*-**6** was isolated which shows that the observed selectivities are indeed a direct consequence of the helical chiral nature of the polymer. At this point it is important to note that the investment of chiral nonracemic material (here **4**) is extremely low. In the ideal case a polymerization reaction, in which one mole of chiral initiator is employed, produces *n* moles of homochiral coordination sites in the resulting polymer. The whole process can be interpreted as an autoinductive multiplication of chiral units. Furthermore, different helical ligands exhibiting different chiral environments can be synthesized by using the same cheap auxiliary.

To learn more about the complexed polymers we studied their chiroptical properties and their NMR spectra. From the CD spectra it is obvious that complexation took place without disrupting the helical chiral structure of the polymers (Figure 1). When we calculated the molar masses of the repeating units with a [N]:[Pd] ratio of 1:1, the chiroptical properties of the palladium complexes became close to those of the uncomplexed polymers. This appears to be reasonable if one assumes that the carbonyl chromophore, which gives rise to the absorption at 237 nm, is largely unaffected by the palladium complexation involving the nitrogen atom of the remote pyridine ring. This interpretation is corroborated by our NMR results (Figure 2).

To study the influence of the polymerization process as well as the one evoked by complexation we recorded a series of

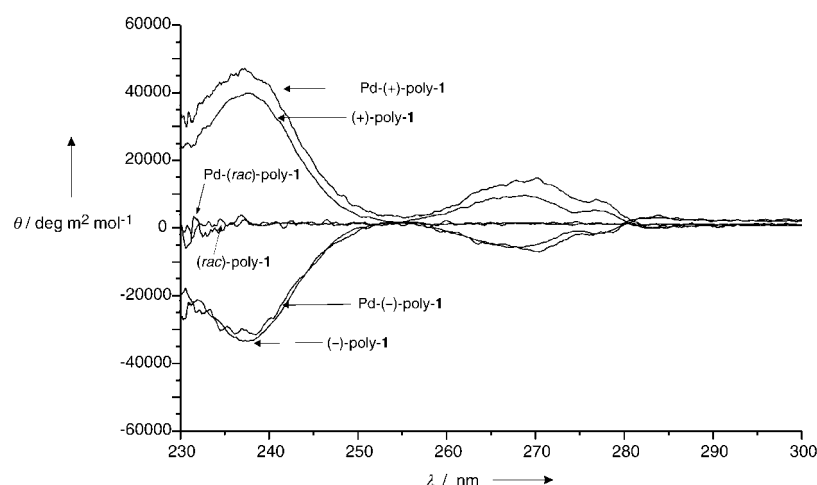


Figure 1. CD spectra of poly-**1** and the corresponding palladium complexes. The CD spectra were recorded in CH₂Cl₂ solutions at 25 °C with polymer concentrations of 37.2 to 78.8 nmol monomer units mL⁻¹.

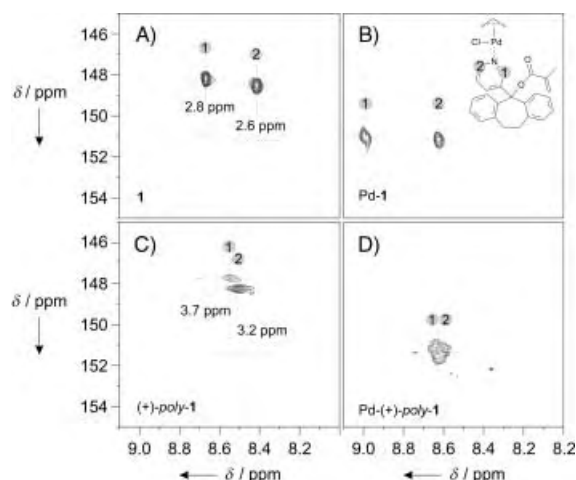


Figure 2. Downfield portion of 500 MHz sensitivity-enhanced gradient-HSQC spectra showing CH correlations of the carbon atoms flanking the nitrogen atom. A) Monomeric **1**. B) Monomeric Pd complex. C) Polymeric **1**. D) Polymeric Pd complex.

HSQC spectra. From these it is obvious that the polymerization of **1** entails a strong reduction of the ¹H chemical shift difference of the protons flanking the nitrogen atom (Figure 2, cf. A and C as well as B and D; $\Delta\delta = 0.22$ ppm and 0.37 ppm, respectively). On the other hand the corresponding carbon shifts are only marginally affected. In contradiction to this behavior, complexation by palladium ([N]:[Pd] = 1:1) is accompanied by a significant downfield shift of carbon atoms 1 and 2. This is true for both the monomeric and the polymeric complex (Figure 2A, 2B, and 2C, 2D, respectively). We interpret these chemical shift alterations as evidence of successful complexation of the polymer by palladium. When we increased the [N]:[Pd] ratio to 2:1 (not shown) the complexation was incomplete as indicated by the persistence of signals from the uncomplexed polymer. This finding is in accordance with a monodentate complex which corroborates our interpretation of the results from the CD data.

From these results it can be concluded that poly-**1** forms monodentate complexes with palladium and that the resulting complex is able to catalyze the allylic substitution reaction. Furthermore the enantiomeric excesses of the products are a direct and sole consequence of the uniform helicity of the polymeric ligand employed. Thus, it is the first example of an asymmetric induction in a catalytic C–C bond forming reaction that involves a uniformly configured polymeric helical chiral ligand lacking any other elements of chirality. Although this is an encouraging first step we are aware that the system must be improved considerably with respect to both reactivity and enantioselectivity. At present, we are working on ligands with alternative coordination sites and the exploitation of the already mentioned cooperative effects in polyisocyanates.

Received: February 5, 2002 [Z18660]

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